

=> d his ful

(FILE 'HOME' ENTERED AT 10:47:08 ON 07 NOV 2005)

FILE 'HCAPLUS' ENTERED AT 10:47:17 ON 07 NOV 2005

E US2003-628141/APPS

L1 2 SEA ABB=ON PLU=ON US2003-628141/AP
SEL RN

FILE 'REGISTRY' ENTERED AT 10:48:10 ON 07 NOV 2005

L2 19 SEA ABB=ON PLU=ON (106650-56-0/BI OR 50-67-9/BI OR 51-41-2/BI
OR 92623-85-3/BI OR 104632-26-0/BI OR 148553-50-8/BI OR
19794-93-5/BI OR 27203-92-5/BI OR 298-46-4/BI OR 300-62-9/BI
OR 4205-90-7/BI OR 439-14-5/BI OR 51-61-6/BI OR 51322-75-9/BI
OR 57-27-2/BI OR 59-92-7/BI OR 60142-96-3/BI OR 76-57-3/BI OR
765-30-0/BI)

FILE 'HCAPLUS' ENTERED AT 10:48:17 ON 07 NOV 2005

L3 2 SEA ABB=ON PLU=ON L1 AND L2
D IALL HITSTR 1-2

FILE 'REGISTRY' ENTERED AT 10:55:53 ON 07 NOV 2005

E MILNACIPRIN/CN

E MILNACIP/CN

L4 1 SEA ABB=ON PLU=ON MILNACIPRAN/CN
D

E SEBRITRAMIN/CN

E SEBRI/CN

E SIBRIT/CN

E SETRITRA/CN

E SEBIT/CN

L*** DEL 0 S L2 AND SEB?/CN

L*** DEL 1 S L2 AND SET?/CN
D KWIC

L*** DEL 1 S L2 AND SET?/CN

L*** DEL 2 S L2 AND SIB?/CN
D KWIC 1-2

L5 1 SEA ABB=ON PLU=ON SIBUTRAMINE/CN
D

E BICIFADINE/CN

L6 1 SEA ABB=ON PLU=ON BICIFADINE/CN
D

E VENLAFAXINE/CN

L7 1 SEA ABB=ON PLU=ON VENLAFAXINE/CN
D

E DULOXEFINE/CN

L8 1 SEA ABB=ON PLU=ON DULOXETINE/CN
D

L9 0 SEA ABB=ON PLU=ON MILNACIPRIN?/CN

L10 2 SEA ABB=ON PLU=ON MILNACIPRAN?/CN

L11 15 SEA ABB=ON PLU=ON SIBUTRAMIN?

L12 2 SEA ABB=ON PLU=ON BICIFADIN?/CN

L13 4 SEA ABB=ON PLU=ON VENLAFAXIN?/CN

L14 3 SEA ABB=ON PLU=ON DULOXETIN?/CN

FILE 'HCAPLUS' ENTERED AT 11:05:31 ON 07 NOV 2005

L15 1525 SEA ABB=ON PLU=ON (L10 OR L11 OR L12 OR L13 OR L14) (L) (BAC
OR DMA OR PAC OR PKT OR THU)/RL
E DEPRESSION/CT


```

      E E3+ALL
      E E2+ALL
L16    10175 SEA ABB=ON  PLU=ON  "MENTAL DISORDER (L) DEPRESSION"+PFT/CT
L17    305 SEA ABB=ON  PLU=ON  L15 AND L16
L18    227 SEA ABB=ON  PLU=ON  (L10 OR L11 OR L12 OR L13 OR L14) (L)DEPRESS
      ?
L19    163 SEA ABB=ON  PLU=ON  L15 AND L18 AND L16
L*** DEL 1 S L1 AND L19
L20    224 SEA ABB=ON  PLU=ON  L10 (L) (BAC OR DMA OR PAC OR PKT OR THU)/RL

L21    65 SEA ABB=ON  PLU=ON  L20 AND L16
L22    47 SEA ABB=ON  PLU=ON  L10 (L)DEPRES?
L23    38 SEA ABB=ON  PLU=ON  L20 AND L16 AND L22
L24    444 SEA ABB=ON  PLU=ON  L11 (L) (BAC OR DMA OR PAC OR PKT OR THU)/RL

L25    11 SEA ABB=ON  PLU=ON  L11 (L)DEPRESS?
L26    9 SEA ABB=ON  PLU=ON  L24 AND L25 AND L16
L27    0 SEA ABB=ON  PLU=ON  L12 (L)DEPRES?
L28    7 SEA ABB=ON  PLU=ON  L12 (L) (BAC OR DMA OR PAC OR PKT OR THU)/RL

L29    1 SEA ABB=ON  PLU=ON  L28 AND L16
L30    878 SEA ABB=ON  PLU=ON  L13 (L) (BAC OR DMA OR PAC OR PKT OR THU)/RL

L31    166 SEA ABB=ON  PLU=ON  L13 (L)DEPRES?
L32    110 SEA ABB=ON  PLU=ON  L30 AND L16 AND L31
L33    242 SEA ABB=ON  PLU=ON  L14 (L) (BAC OR DMA OR PAC OR PKT OR THU)/RL

L34    39 SEA ABB=ON  PLU=ON  L14 (L)DEPRES?
L35    68 SEA ABB=ON  PLU=ON  L33 AND L16
L36    35 SEA ABB=ON  PLU=ON  L35 AND L34
      E DSP/CT
      E E3+ALL
      E DEPRESSION SECONDARY TO PAIN/CT
      E DEPRESSION/CT
      E E3+ALL
      E E2+ALL
L37    40 SEA ABB=ON  PLU=ON  MENTAL DISORDER+PFT/CT (L) SECONDARY
L38    149 SEA ABB=ON  PLU=ON  MENTAL DISORDER+PFT/CT (L) PAIN
L39    3 SEA ABB=ON  PLU=ON  L37 AND L38
L40    3 SEA ABB=ON  PLU=ON  L39 AND L16
      D SCA
L41    2 SEA ABB=ON  PLU=ON  L40 AND (L10 OR L11 OR L12 OR L13 OR L14)
L42    2 SEA ABB=ON  PLU=ON  ?DEPRESS? (5A) ?SECONDAR? (2A) ?PAIN?
      D SCA
L43    2 SEA ABB=ON  PLU=ON  L42 OR L41
      E NSRI/CT
      E NOREPINEPHRINE SEROTONIN REUPTAKE/CT
      E E2+ALL
      E E2+ALL
L44    203 SEA ABB=ON  PLU=ON  "NERVOUS SYSTEM AGENTS (L) NORADRENALINE
      REUPTAKE INHIBITORS"+PFT/CT
L45    459 SEA ABB=ON  PLU=ON  L44 OR NSRI OR NOREPINEP? (2A) SEROTONIN (5A) R
      EUPT? (5A) (INHIB? OR BLOCK? OR ANTAG?)
      E TRIPLE REUP/CT
      E TRI/CT
L46    219109 SEA ABB=ON  PLU=ON  TRI OR TRIPLE (3A) REUP? (3A) (INHIB? OR
      BLOCK? OR ANTAG?)
L47    9 SEA ABB=ON  PLU=ON  TRIPLE (3A) REUP? (3A) (INHIB? OR BLOCK? OR
      ANTAG?)

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L48 463 SEA ABB=ON PLU=ON L47 OR L45
 L49 76 SEA ABB=ON PLU=ON L48 AND (DSP OR (?DEPRESS? AND ?PAIN?))
 L50 37 SEA ABB=ON PLU=ON L48 AND (DSP OR (?DEPRESS?(10A)?PAIN?))

 FILE 'MEDLINE' ENTERED AT 11:28:35 ON 07 NOV 2005
 L51 1416 SEA ABB=ON PLU=ON (L10 OR L11 OR L12 OR L13 OR L14)
 E DEPRESSION SECONDARY TO PAIN/CT
 L52 0 SEA ABB=ON PLU=ON "DEPRESSION SECONDARY TO PAIN"
 E DEPRESSION/CT
 E E3+ALL
 L53 37791 SEA ABB=ON PLU=ON DEPRESSION+PFT/CT
 E E16+ALL
 L54 28215 SEA ABB=ON PLU=ON ANTIDEPRESSIVE AGENTS+PFT/CT
 L55 61875 SEA ABB=ON PLU=ON L54 OR L53
 L56 749 SEA ABB=ON PLU=ON L51 AND L55
 L*** DEL 0 S L10-14(3A)?DEPRES?
 L*** DEL 0 S L10-14(10A)?DEPRES?
 L*** DEL 0 S L10-14(S)?DEPRES?
 L*** DEL 0 S L10-14(L)?DEPRES?
 L57 48 SEA ABB=ON PLU=ON L53 AND L54 AND L51
 E DSP/CT
 L58 1426 SEA ABB=ON PLU=ON DSP OR ?DEPRES?(5A)?SECONDAR?(5A)?PAIN?
 D SCA
 D TRIAL
 D KWIC 1 200 300
 L59 12 SEA ABB=ON PLU=ON ?DEPRES?(5A)?SECONDAR?(5A)?PAIN?
 D SCA
 D TRIAL
 D KWIC 1-3
 L60 0 SEA ABB=ON PLU=ON L59 AND L51
 E NSRI/CT
 E NOREPINEPHRINE SEROTONIN REUP/CT
 E NOREPINEPHRINE REUP/CT
 E REUPTAKE/CT
 E E7+ALL
 E E2+ALL
 L61 702 SEA ABB=ON PLU=ON NOREPINEPHRIN?(5A)SEROTON? AND ?UPTAK?(3A) I
 NHIB?
 D KWIC
 E TRIPLE REUP/CT
 L62 4 SEA ABB=ON PLU=ON TRIPLE?(3A)?UPTAK?(5A)INHIB?
 L63 704 SEA ABB=ON PLU=ON L61 OR L62
 L64 69 SEA ABB=ON PLU=ON L63 AND ?PAIN?
 L65 56 SEA ABB=ON PLU=ON L64 AND ?DEPRES?
 D KWIC

FILE 'EMBASE' ENTERED AT 11:42:14 ON 07 NOV 2005
 L66 6976 SEA ABB=ON PLU=ON (L10 OR L11 OR L12 OR L13 OR L14)
 E DEPRESSION/CT
 E E3+ALL
 L67 117816 SEA ABB=ON PLU=ON DEPRESSION+PFT/CT
 E ANTIDEPRESS/CT
 E E6+ALL
 L68 134932 SEA ABB=ON PLU=ON ANTIDEPRESSANT AGENT+PFT/CT
 L69 3693 SEA ABB=ON PLU=ON L66 AND L67 AND L68
 E DEPRESSION SECONDARY TO PAIN/CT
 L70 23 SEA ABB=ON PLU=ON ?DEPRESS?(5A)?SECOND?(5A)?PAIN?
 D KWIC
 L71 14 SEA ABB=ON PLU=ON ?DEPRESS?(5A)?SECONDAR?(5A)?PAIN?

L72 D KWIC
1 SEA ABB=ON PLU=ON L71 AND L66
D KWIC
E NSRI/CT
L73 497 SEA ABB=ON PLU=ON NOREPINEPH? (5A) SEROTON? (10A) ?UPTAK? (3A) INHI
B?
L74 6 SEA ABB=ON PLU=ON TRIPLE (5A) ?UPTAK? (5A) INHIB?
L75 501 SEA ABB=ON PLU=ON L73 OR L74
L76 68 SEA ABB=ON PLU=ON L75 AND ?PAIN?
L77 53 SEA ABB=ON PLU=ON L76 AND ?DEPRES?
D TRIAL
L78 20 SEA ABB=ON PLU=ON L75 AND ?PAIN? (5A) ?DEPRES?

FILE 'WPIX' ENTERED AT 11:49:30 ON 07 NOV 2005
L79 553 SEA ABB=ON PLU=ON ?MILNACIPRA? OR ?SIBUTRAMIN? OR ?BICIFADIN?
OR ?VENLAFAXIN? OR ?DULOXETIN?
L80 1 SEA ABB=ON PLU=ON L79 AND ?PAIN? (5A) ?SECONDA? (5A) ?DEPRES?
L81 317 SEA ABB=ON PLU=ON L79 AND ?DEPRES?
L82 197 SEA ABB=ON PLU=ON SEROTON? (5A) NOREPINEPH? (10A) ?UPTAK? (3A) INHI
B?
L83 5 SEA ABB=ON PLU=ON TRIPLE? (5A) ?UPTAK? (3A) ?INHIB?
L84 198 SEA ABB=ON PLU=ON L82 OR L83
L85 34 SEA ABB=ON PLU=ON L84 AND ?PAIN? (5A) ?DEPRES?

FILE 'HCAPLUS' ENTERED AT 11:59:30 ON 07 NOV 2005

FILE HOME

FILE HCAPLUS

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FILE COVERS 1907 - 7 Nov 2005 VOL 143 ISS 20
FILE LAST UPDATED: 6 Nov 2005 (20051106/ED)

New CAS Information Use Policies, enter HELP USAGETERMS for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

FILE REGISTRY

Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 6 NOV 2005 HIGHEST RN 866821-44-5
DICTIONARY FILE UPDATES: 6 NOV 2005 HIGHEST RN 866821-44-5

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH JULY 14, 2005

Please note that search-term pricing does apply when conducting SmartSELECT searches.

*
* The CA roles and document type information have been removed from *
* the IDE default display format and the ED field has been added, *
* effective March 20, 2005. A new display format, IDERL, is now *
* available and contains the CA role and document type information. *
*

Structure search iteration limits have been increased. See HELP SLIMITS for details.

REGISTRY includes numerically searchable data for experimental and predicted properties as well as tags indicating availability of experimental property data in the original document. For information on property searching in REGISTRY, refer to:

<http://www.cas.org/ONLINE/UG/regprops.html>

FILE MEDLINE

FILE LAST UPDATED: 5 NOV 2005 (20051105/UP). FILE COVERS 1950 TO DATE.

On December 19, 2004, the 2005 MeSH terms were loaded.

The MEDLINE reload for 2005 is now available. For details enter HELP RLOAD at an arrow prompt (=>). See also:

<http://www.nlm.nih.gov/mesh/>
http://www.nlm.nih.gov/pubs/techbull/nd04/nd04_mesh.html

OLDMEDLINE now back to 1950.

MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the MeSH 2005 vocabulary.

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FILE EMBASE

FILE COVERS 1974 TO 3 Nov 2005 (20051103/ED)

EMBASE has been reloaded. Enter HELP RLOAD for details.

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FILE WPIX

FILE LAST UPDATED: 4 NOV 2005 <20051104/UP>
MOST RECENT DERWENT UPDATE: 200571 <200571/DW>
DERWENT WORLD PATENTS INDEX SUBSCRIBER FILE, COVERS 1963 TO DATE

>>> FOR A COPY OF THE DERWENT WORLD PATENTS INDEX STN USER GUIDE,
PLEASE VISIT:
http://www.stn-international.de/training_center/patents/stn_guide.pdf <<<

>>> FOR DETAILS OF THE PATENTS COVERED IN CURRENT UPDATES, SEE
<http://thomsonderwent.com/coverage/latestupdates/> <<<

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DOCUMENTATION NOW AVAILABLE IN DERWENT WORLD PATENTS INDEX
FIRST VIEW - FILE WPIFV.
FOR FURTHER DETAILS: <http://www.thomsonderwent.com/dwpifv> <<<

>>> THE CPI AND EPI MANUAL CODES HAVE BEEN REVISED FROM UPDATE 200501.
PLEASE CHECK:
<http://thomsonderwent.com/support/dwpioref/reftools/classification/code-rev>
FOR DETAILS. <<<

=> fil hcap
FILE 'HCAPLUS' ENTERED AT 11:59:42 ON 07 NOV 2005
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FILE COVERS 1907 - 7 Nov 2005 VOL 143 ISS 20
FILE LAST UPDATED: 6 Nov 2005 (20051106/ED)

New CAS Information Use Policies, enter HELP USAGETERMS for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> d que stat 123
L10 2 SEA FILE=REGISTRY ABB=ON PLU=ON MILNACIPRAN?/CN
L16 10175 SEA FILE=HCAPLUS ABB=ON PLU=ON "MENTAL DISORDER (L) DEPRESSIO
N"+PFT/CT
L20 224 SEA FILE=HCAPLUS ABB=ON PLU=ON L10(L) (BAC OR DMA OR PAC OR
PKT OR THU)/RL
L22 47 SEA FILE=HCAPLUS ABB=ON PLU=ON L10(L)DEPRES?
L23 38 SEA FILE=HCAPLUS ABB=ON PLU=ON L20 AND L16 AND L22

=> d que stat 126
L11 15 SEA FILE=REGISTRY ABB=ON PLU=ON SIBUTRAMIN?
L16 10175 SEA FILE=HCAPLUS ABB=ON PLU=ON "MENTAL DISORDER (L) DEPRESSIO
N"+PFT/CT
L24 444 SEA FILE=HCAPLUS ABB=ON PLU=ON L11(L) (BAC OR DMA OR PAC OR
PKT OR THU)/RL
L25 11 SEA FILE=HCAPLUS ABB=ON PLU=ON L11(L)DEPRESS?

L26 9 SEA FILE=HCAPLUS ABB=ON PLU=ON L24 AND L25 AND L16

=> d que stat 129

L12 2 SEA FILE=REGISTRY ABB=ON PLU=ON BICIFADIN?/CN
 L16 10175 SEA FILE=HCAPLUS ABB=ON PLU=ON "MENTAL DISORDER (L) DEPRESSIO
 N"+PFT/CT
 L28 7 SEA FILE=HCAPLUS ABB=ON PLU=ON L12 (L) (BAC OR DMA OR PAC OR
 PKT OR THU)/RL
 L29 1 SEA FILE=HCAPLUS ABB=ON PLU=ON L28 AND L16

=> d que stat 132

L13 4 SEA FILE=REGISTRY ABB=ON PLU=ON VENLAFAXIN?/CN
 L16 10175 SEA FILE=HCAPLUS ABB=ON PLU=ON "MENTAL DISORDER (L) DEPRESSIO
 N"+PFT/CT
 L30 878 SEA FILE=HCAPLUS ABB=ON PLU=ON L13 (L) (BAC OR DMA OR PAC OR
 PKT OR THU)/RL
 L31 166 SEA FILE=HCAPLUS ABB=ON PLU=ON L13 (L) DEPRES?
 L32 110 SEA FILE=HCAPLUS ABB=ON PLU=ON L30 AND L16 AND L31

=> d que stat 136

L14 3 SEA FILE=REGISTRY ABB=ON PLU=ON DULOXETIN?/CN
 L16 10175 SEA FILE=HCAPLUS ABB=ON PLU=ON "MENTAL DISORDER (L) DEPRESSIO
 N"+PFT/CT
 L33 242 SEA FILE=HCAPLUS ABB=ON PLU=ON L14 (L) (BAC OR DMA OR PAC OR
 PKT OR THU)/RL
 L34 39 SEA FILE=HCAPLUS ABB=ON PLU=ON L14 (L) DEPRES?
 L35 68 SEA FILE=HCAPLUS ABB=ON PLU=ON L33 AND L16
 L36 35 SEA FILE=HCAPLUS ABB=ON PLU=ON L35 AND L34

=> s 123 or 126 or 129 or 132 or 136

L86 164 L23 OR L26 OR L29 OR L32 OR L36

=> d que stat 143

L10 2 SEA FILE=REGISTRY ABB=ON PLU=ON MILNACIPRAN?/CN
 L11 15 SEA FILE=REGISTRY ABB=ON PLU=ON SIBUTRAMIN?
 L12 2 SEA FILE=REGISTRY ABB=ON PLU=ON BICIFADIN?/CN
 L13 4 SEA FILE=REGISTRY ABB=ON PLU=ON VENLAFAXIN?/CN
 L14 3 SEA FILE=REGISTRY ABB=ON PLU=ON DULOXETIN?/CN
 L16 10175 SEA FILE=HCAPLUS ABB=ON PLU=ON "MENTAL DISORDER (L) DEPRESSIO
 N"+PFT/CT
 L37 40 SEA FILE=HCAPLUS ABB=ON PLU=ON MENTAL DISORDER+PFT/CT (L) SECON
 DARY
 L38 149 SEA FILE=HCAPLUS ABB=ON PLU=ON MENTAL DISORDER+PFT/CT (L) PAIN
 L39 3 SEA FILE=HCAPLUS ABB=ON PLU=ON L37 AND L38
 L40 3 SEA FILE=HCAPLUS ABB=ON PLU=ON L39 AND L16
 L41 2 SEA FILE=HCAPLUS ABB=ON PLU=ON L40 AND (L10 OR L11 OR L12 OR
 L13 OR L14)
 L42 2 SEA FILE=HCAPLUS ABB=ON PLU=ON ?DEPRESS? (5A) ?SECONDAR? (2A) ?PA
 IN?
 L43 2 SEA FILE=HCAPLUS ABB=ON PLU=ON L42 OR L41

=> d que stat 150

L44 203 SEA FILE=HCAPLUS ABB=ON PLU=ON "NERVOUS SYSTEM AGENTS (L)


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                NORADRENALINE REUPTAKE INHIBITORS"+PFT/CT
L45          459 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L44 OR NSRI OR NOREPINEP?(2A)S
                EROTONIN(5A)REUPT?(5A)(INHIB? OR BLOCK? OR ANTAG?)
L47           9 SEA FILE=HCAPLUS ABB=ON  PLU=ON  TRIPLE(3A)REUP?(3A)(INHIB? OR
                BLOCK? OR ANTAG?)
L48          463 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L47 OR L45
L50          37 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L48 AND (DSP OR (?DEPRESS?(10A
                )?PAIN?))

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=> s l86 or l43 or l50
L87          192 L86 OR L43 OR L50

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=> fil medline
FILE 'MEDLINE' ENTERED AT 12:01:00 ON 07 NOV 2005

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FILE LAST UPDATED: 5 NOV 2005 (20051105/UP). FILE COVERS 1950 TO DATE.

On December 19, 2004, the 2005 MeSH terms were loaded.

The MEDLINE reload for 2005 is now available. For details enter HELP
RLOAD at an arrow prompt (=>). See also:

```

http://www.nlm.nih.gov/mesh/
http://www.nlm.nih.gov/pubs/techbull/nd04/nd04_mesh.html

```

OLDMEDLINE now back to 1950.

MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the
MeSH 2005 vocabulary.

This file contains CAS Registry Numbers for easy and accurate
substance identification.

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=> d que stat l57
L10           2 SEA FILE=REGISTRY ABB=ON  PLU=ON  MILNACIPRAN?/CN
L11          15 SEA FILE=REGISTRY ABB=ON  PLU=ON  SIBUTRAMIN?
L12           2 SEA FILE=REGISTRY ABB=ON  PLU=ON  BICIFADIN?/CN
L13           4 SEA FILE=REGISTRY ABB=ON  PLU=ON  VENLAFAXIN?/CN
L14           3 SEA FILE=REGISTRY ABB=ON  PLU=ON  DULOXETIN?/CN
L51          1416 SEA FILE=MEDLINE ABB=ON  PLU=ON  (L10 OR L11 OR L12 OR L13 OR
                L14)
L53          37791 SEA FILE=MEDLINE ABB=ON  PLU=ON  DEPRESSION+PFT/CT
L54          28215 SEA FILE=MEDLINE ABB=ON  PLU=ON  ANTIDEPRESSIVE AGENTS+PFT/CT
L57           48 SEA FILE=MEDLINE ABB=ON  PLU=ON  L53 AND L54 AND L51

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=> d que stat l60
L10           2 SEA FILE=REGISTRY ABB=ON  PLU=ON  MILNACIPRAN?/CN
L11          15 SEA FILE=REGISTRY ABB=ON  PLU=ON  SIBUTRAMIN?
L12           2 SEA FILE=REGISTRY ABB=ON  PLU=ON  BICIFADIN?/CN
L13           4 SEA FILE=REGISTRY ABB=ON  PLU=ON  VENLAFAXIN?/CN
L14           3 SEA FILE=REGISTRY ABB=ON  PLU=ON  DULOXETIN?/CN
L51          1416 SEA FILE=MEDLINE ABB=ON  PLU=ON  (L10 OR L11 OR L12 OR L13 OR
                L14)
L59           12 SEA FILE=MEDLINE ABB=ON  PLU=ON  ?DEPRES?(5A)?SECONDAR?(5A)?PAI
                N?
L60           0 SEA FILE=MEDLINE ABB=ON  PLU=ON  L59 AND L51

```


=> d que stat l65

```
L61          702 SEA FILE=MEDLINE ABB=ON  PLU=ON  NOREPINEPHRIN? (5A) SEROTON?
              AND ?UPTAK? (3A) INHIB?
L62           4 SEA FILE=MEDLINE ABB=ON  PLU=ON  TRIPLE? (3A) ?UPTAK? (5A) INHIB?
L63          704 SEA FILE=MEDLINE ABB=ON  PLU=ON  L61 OR L62
L64           69 SEA FILE=MEDLINE ABB=ON  PLU=ON  L63 AND ?PAIN?
L65           56 SEA FILE=MEDLINE ABB=ON  PLU=ON  L64 AND ?DEPRES?
```

=> s l57 or l65

L88 104 L57 OR L65

=> fil embase

FILE 'EMBASE' ENTERED AT 12:01:30 ON 07 NOV 2005

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FILE COVERS 1974 TO 3 Nov 2005 (20051103/ED)

EMBASE has been reloaded. Enter HELP RLOAD for details.

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=> d que stat l72

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L10           2 SEA FILE=REGISTRY ABB=ON  PLU=ON  MILNACIPRAN?/CN
L11          15 SEA FILE=REGISTRY ABB=ON  PLU=ON  SIBUTRAMIN?
L12           2 SEA FILE=REGISTRY ABB=ON  PLU=ON  BICIFADIN?/CN
L13           4 SEA FILE=REGISTRY ABB=ON  PLU=ON  VENLAFAXIN?/CN
L14           3 SEA FILE=REGISTRY ABB=ON  PLU=ON  DULOXETIN?/CN
L66          6976 SEA FILE=EMBASE ABB=ON  PLU=ON  (L10 OR L11 OR L12 OR L13 OR
              L14)
L71          14 SEA FILE=EMBASE ABB=ON  PLU=ON  ?DEPRESS? (5A) ?SECONDAR? (5A) ?PAI
              N?
L72           1 SEA FILE=EMBASE ABB=ON  PLU=ON  L71 AND L66
```

=> d que stat l78

```
L73          497 SEA FILE=EMBASE ABB=ON  PLU=ON  NOREPINEPH? (5A) SEROTON? (10A) ?UP
              TAK? (3A) INHIB?
L74           6 SEA FILE=EMBASE ABB=ON  PLU=ON  TRIPLE (5A) ?UPTAK? (5A) INHIB?
L75          501 SEA FILE=EMBASE ABB=ON  PLU=ON  L73 OR L74
L78          20 SEA FILE=EMBASE ABB=ON  PLU=ON  L75 AND ?PAIN? (5A) ?DEPRES?
```

=> s l72 or l78

L89 21 L72 OR L78

=> fil wpix

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=> d que stat 180
L79 553 SEA FILE=WPIX ABB=ON PLU=ON ?MILNACIPRA? OR ?SIBUTRAMIN? OR
?BICIFADIN? OR ?VENLAFAXIN? OR ?DULOXETIN?
L80 1 SEA FILE=WPIX ABB=ON PLU=ON L79 AND ?PAIN? (5A) ?SECONDAR? (5A) ?
DEPRES?

=> d que stat 185
L82 197 SEA FILE=WPIX ABB=ON PLU=ON SEROTON? (5A) NOREPINEPH? (10A) ?UPTA
K? (3A) INHIB?
L83 5 SEA FILE=WPIX ABB=ON PLU=ON TRIPLE? (5A) ?UPTAK? (3A) ?INHIB?
L84 198 SEA FILE=WPIX ABB=ON PLU=ON L82 OR L83
L85 34 SEA FILE=WPIX ABB=ON PLU=ON L84 AND ?PAIN? (5A) ?DEPRES?

=> s 180 or 185
L90 34 L80 OR L85

=> dup rem 188 187 189 190
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PROCESSING COMPLETED FOR L88
PROCESSING COMPLETED FOR L87
PROCESSING COMPLETED FOR L89
PROCESSING COMPLETED FOR L90
L91 313 DUP REM L88 L87 L89 L90 (38 DUPLICATES REMOVED)
ANSWERS '1-104' FROM FILE MEDLINE
ANSWERS '105-282' FROM FILE HCAPLUS
ANSWERS '283-288' FROM FILE EMBASE
ANSWERS '289-313' FROM FILE WPIX

=> d 191 ibib ab hitind 1-313

L91 ANSWER 1 OF 313 MEDLINE on STN DUPLICATE 3
ACCESSION NUMBER: 2005253349 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15892657
TITLE: The dual transporter inhibitor duloxetine: a review of its
preclinical pharmacology, pharmacokinetic profile, and
clinical results in **depression**.
AUTHOR: Bymaster Frank P; Lee Thomas C; Knadler Mary Pat; Detke
Michael J; Iyengar Smriti
CORPORATE SOURCE: Lilly Research Laboratories, Eli Lilly and Company,
Indianapolis, IN, USA.
SOURCE: Current pharmaceutical design, (2005) 11 (12) 1475-93.
Ref: 132
Journal code: 9602487. ISSN: 1381-6128.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200506
ENTRY DATE: Entered STN: 20050517
Last Updated on STN: 20050603
Entered Medline: 20050602
AB Major **depressive** disorder (MDD) poses a significant health
problem and is estimated to be the third most costly and disabling
disorder in the United States. Pharmacotherapy of **depression**
has been successful, but improvements in response rates, remission rates,
side effects, compliance and faster onset of therapeutic action have
become prime objectives in drug development. There is considerable
support for the hypothesis that dysfunctional serotonergic or
noradrenergic neurotransmission may be etiological in **depressed**
patients. Duloxetine is a balanced and potent **reuptake**
inhibitor of **serotonin** (5-HT) and **norepinephrine**
(NE) being studied as an **antidepressant** medication. In this
review, we highlight the preclinical pharmacology, pharmacokinetic
profile, and effects of duloxetine in the pharmacotherapy of
depression. Evidence for 5-HT and NE **reuptake**
inhibition by duloxetine comes from in vitro and in vivo
transporter binding and functional uptake studies. Taken together with
efficacy data from in vivo microdialysis, electrophysiological and
behavioral studies, it is evident that duloxetine is balanced as a dual
serotonin norepinephrine uptake
inhibitor in vivo. The clinical efficacy and safety of duloxetine
in the treatment of MDD has been studied in 6 multicenter, randomized,
double-blind, placebo-controlled trials. In these studies, duloxetine was
found to be effective in the treatment of emotional/psychological and
painful physical symptoms associated with **depression**.
More importantly, duloxetine appears to have better response rates and
remission from **depressive** symptoms, perhaps due to its ability
to treat a wider range of symptoms.
CT ***Adrenergic Uptake Inhibitors**: PD, pharmacology
Animals
***Antidepressive Agents**: PD, pharmacology
***Depression**: DT, drug therapy
***Depressive Disorder, Major**: DT, drug therapy
Humans
Microdialysis

Research Support, Non-U.S. Gov't

***Serotonin Uptake Inhibitors: PD, pharmacology**

Thiophenes: AE, adverse effects

Thiophenes: PK, pharmacokinetics

*Thiophenes: PD, pharmacology

Thiophenes: TU, therapeutic use

RN 116539-58-3 (duloxetine)

CN 0 (Adrenergic **Uptake Inhibitors**); 0 (**Antidepressive Agents**); 0 (**Serotonin Uptake Inhibitors**); 0 (Thiophenes)

L91 ANSWER 2 OF 313 MEDLINE on STN DUPLICATE 4
ACCESSION NUMBER: 2005471503 IN-PROCESS
DOCUMENT NUMBER: PubMed ID: 16142213
TITLE: SNRIs: their pharmacology, clinical efficacy, and tolerability in comparison with other classes of **antidepressants**.
AUTHOR: Stahl Stephen M; Grady Meghan M; Moret Chantal; Briley Mike
CORPORATE SOURCE: Department of Psychiatry, University of California, San Diego, San Diego, CA, USA.
SOURCE: CNS spectrums, (2005 Sep) 10 (9) 732-47.
Journal code: 9702877. ISSN: 1092-8529.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: NONMEDLINE; IN-PROCESS; NONINDEXED; Priority Journals
ENTRY DATE: Entered STN: 20050907
Last Updated on STN: 20051026

AB The class of **serotonin and norepinephrine reuptake inhibitors** (SNRIs) now comprises three medications: venlafaxine, milnacipran, and duloxetine. These drugs block the reuptake of both **serotonin** (5-HT) and **norepinephrine** with differing selectivity. Whereas milnacipran blocks 5-HT and norepinephrine reuptake with equal affinity, duloxetine has a 10-fold selectivity for 5-HT and venlafaxine a 30-fold selectivity for 5-HT. All three SNRIs are efficacious in treating a variety of anxiety disorders. There is no evidence for major differences between SNRIs and SSRIs in their efficacy in treating anxiety disorders. In contrast to SSRIs, which are generally ineffective in treating chronic **pain**, all three SNRIs seem to be helpful in relieving chronic **pain** associated with and independent of **depression**. Tolerability of an SNRI at therapeutic doses varies within the class. Although no direct comparative data are available, venlafaxine seems to be the least well-tolerated, combining serotonergic adverse effects (nausea, sexual dysfunction, withdrawal problems) with a dose-dependent cardiovascular phenomenon, principally hypertension. Duloxetine and milnacipran appear better tolerated and essentially devoid of cardiovascular toxicity.

L91 ANSWER 3 OF 313 MEDLINE on STN DUPLICATE 5
ACCESSION NUMBER: 2005209497 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15843287
TITLE: Duloxetine: a dual **serotonin-norepinephrine reuptake inhibitor** for treatment of major **depressive** disorder.
AUTHOR: Kirwin Jennifer L; Goren Jessica L
CORPORATE SOURCE: Department of Pharmacy Practice, Bouve College of Health Sciences, Northeastern University, Boston, Massachusetts, USA.
SOURCE: Pharmacotherapy, (2005 Mar) 25 (3) 396-410. Ref: 69

Journal code: 8111305. ISSN: 0277-0008.
 PUB. COUNTRY: United States
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
 General Review; (REVIEW)
 (REVIEW, TUTORIAL)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 200505
 ENTRY DATE: Entered STN: 20050422
 Last Updated on STN: 20050519
 Entered Medline: 20050518

AB The burden of mental illness has been underestimated worldwide. **Depression** was the fourth leading cause of disease burden in the world in 1990 and is projected to be the second leading cause of disability by 2020. It is a leading cause of morbidity and mortality in the United States, costing billions of dollars annually in direct and indirect medical costs and losses in productivity. Patients with major **depressive** disorder (MDD) may experience both psychological and medical complaints, including somatic sensations or **pain**. Some **antidepressants** have been shown to treat chronic **pain** syndromes, but despite the variety of **antidepressants** available in the United States, only 65-70% of patients respond to initial **antidepressant** treatment. Treatments are limited by delayed onset of **antidepressant** effects, side effects, partial response, and treatment resistance. Duloxetine, approved by the U.S. Food and Drug Administration for the treatment of MDD, is a **reuptake inhibitor** at serotonergic and noradrenergic neurons and appears to have low affinity for other neurotransmitter systems. In clinical trials, duloxetine was effective for the treatment of MDD and was well tolerated. Further study is needed to compare its efficacy with that of other **antidepressants**, to clarify effects on somatic symptoms, and to assess potential adverse cardiovascular and sexual side effects. Duloxetine is also approved for the management of diabetic peripheral neuropathic **pain** and is under investigation for the treatment of stress urinary incontinence in women.

CT Adolescent
 Adult
 Aged
 *Depressive Disorder, Major: DT, drug therapy
 Drug Interactions
 Humans
 Middle Aged
 Randomized Controlled Trials
 *Serotonin Uptake Inhibitors: PD, pharmacology
 *Serotonin Uptake Inhibitors: TU, therapeutic use
 *Thiophenes: PD, pharmacology
 *Thiophenes: TU, therapeutic use
 RN 116539-58-3 (duloxetine)
 CN 0 (Serotonin Uptake Inhibitors); 0 (Thiophenes)

L91 ANSWER 4 OF 313 MEDLINE on STN DUPLICATE 6
 ACCESSION NUMBER: 2005148800 MEDLINE
 DOCUMENT NUMBER: PubMed ID: 15780208
 TITLE: Effects of extract of Ginkgo biloba with venlafaxine on brain injury in a rat model of depression.
 AUTHOR: Qin Xiao-song; Jin Kui-he; Ding Bao-kun; Xie Shou-fu; Ma Hui
 CORPORATE SOURCE: Department of Medical Laboratory, Second Affiliated Hospital of China Medical University, Shenyang 110004,

SOURCE: China.. qinxiaosong@hotmail.com
Chinese medical journal, (2005 Mar 5) 118 (5) 391-7.
Journal code: 7513795. ISSN: 0366-6999.

PUB. COUNTRY: China
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200505
ENTRY DATE: Entered STN: 20050323
Last Updated on STN: 20050506
Entered Medline: 20050505

AB BACKGROUND: Recent studies have indicated that chronic stress may give rise to brain damage, which is related to the genesis of depression. The purpose of this study is to investigate the effects of extract of Ginkgo biloba (EGb) and venlafaxine on depression. METHODS: Rats were treated with chronic and comprehensive stress to create a depression model. Immunohistochemistry was used to detect the expression of brain-derived neurotrophic factor (BDNF) in the hippocampal CA3 neurons of rats treated with different drugs. Behavioral changes of these rats were also examined. RESULTS: The expression of BDNF in the hippocampal CA3 neurons of the depression model decreased with a reduction in exploring behavior and a significant increase in fecal production. The expression of neuron nitric-oxide synthase (nNOS) protein also increased in the rats compared to normal controls. The rats treated with EGb and venlafaxine showed an increase in expression of BDNF and exploring behavior compared to untreated rats, but a decrease in nNOS and fecal production. CONCLUSIONS: Rats sustain damage to the brain after being subjected to chronic and comprehensive stress. Our research has indicated that combined EGb with venlafaxine enhances the protection of neurons and decreases damage to the brain, while relieving the side effects of synthetic antidepressants.

CT Check Tags: Male
Animals
Antidepressive Agents, Second-Generation: AD, administration & dosage
*Brain Injuries: CO, complications
Brain Injuries: ME, metabolism
Brain-Derived Neurotrophic Factor: BI, biosynthesis
*Cyclohexanols: AD, administration & dosage
***Depression: DT, drug therapy**
Depression: ET, etiology
Drugs, Chinese Herbal: AD, administration & dosage
*Ginkgo biloba: CH, chemistry
Hippocampus: ME, metabolism
*Phytotherapy
Rats
Rats, Wistar
Research Support, Non-U.S. Gov't

RN **93413-69-5 (venlafaxine)**
CN 0 (Antidepressive Agents, Second-Generation); 0 (Brain-Derived Neurotrophic Factor); 0 (Cyclohexanols); 0 (Drugs, Chinese Herbal)

L91 ANSWER 5 OF 313 MEDLINE on STN DUPLICATE 7
ACCESSION NUMBER: 2005097215 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15728754
TITLE: Duloxetine for the treatment of major depressive disorder in older patients.
AUTHOR: Nelson J Craig; Wohlreich Madelaine M; Mallinckrodt Craig H; Detke Michael J; Watkin John G; Kennedy John S
CORPORATE SOURCE: Department of Psychiatry, University of California at San

SOURCE: Francisco, San Francisco, CA, USA.
American journal of geriatric psychiatry : official journal
of the American Association for Geriatric Psychiatry, (2005
Mar) 13 (3) 227-35.
Journal code: 9309609. ISSN: 1064-7481.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200508
ENTRY DATE: Entered STN: 20050301
Last Updated on STN: 20050815
Entered Medline: 20050811

AB OBJECTIVE: The efficacy and safety of duloxetine, a dual **reuptake inhibitor** of **serotonin** (5-HT) and **norepinephrine** (NE), were evaluated in the treatment of major **depressive** disorder (MDD) and associated **pain** symptoms in patients age 55 and older. METHODS: Efficacy data were obtained from patients age > or =55 who participated in two identical, multicenter, double-blind studies in which patients with MDD were randomized to receive placebo (N=43) or duloxetine (60 mg/day; N=47) for 9 weeks. The primary efficacy measure was the mean change in Ham-D-17 total score. **Pain** symptoms were assessed with visual-analog scales. Safety data for patients age > or =55 were pooled from six randomized, 8- or 9-week, double-blind studies of duloxetine in which patients with MDD were randomized to receive placebo (N=90) or duloxetine (40 mg/day-120 mg/day; N=119). RESULTS: The combined results of these two investigations found that duloxetine was significantly superior to placebo for mean change in Ham-D-17 total score. The estimated probability of remission for duloxetine-treated patients (44.1%) was also significantly higher than that for placebo (16.1%). Reductions in overall **pain**, **back pain**, and **pain** while awake were also significantly greater for duloxetine than placebo. The rate of discontinuation due to adverse events was significantly higher for duloxetine-treated patients (21.0%) than placebo (6.7%). Abnormal elevations in vital signs at endpoint were not significantly different from placebo. CONCLUSIONS: In these two investigations, duloxetine 60 mg/day was an efficacious treatment for MDD and also alleviated **pain** symptoms in **depression** patients age 55 and older.

CT Check Tags: Female; Male
Aged
Aged, 80 and over
Analysis of Variance
*Depressive Disorder, Major: DT, drug therapy
Humans
Middle Aged
Pain: DT, drug therapy
Randomized Controlled Trials
Research Support, Non-U.S. Gov't
Serotonin Uptake Inhibitors: AE, adverse effects
*Serotonin Uptake Inhibitors: TU, therapeutic use
Thiophenes: AE, adverse effects
*Thiophenes: TU, therapeutic use
Treatment Outcome
RN 116539-58-3 (duloxetine)
CN 0 (Serotonin Uptake Inhibitors); 0 (Thiophenes)

L91 ANSWER 6 OF 313 MEDLINE on STN DUPLICATE 8
ACCESSION NUMBER: 2004534233 MEDLINE

DOCUMENT NUMBER: PubMed ID: 15504423
TITLE: Duloxetine 60 mg once-daily in the treatment of **painful** physical symptoms in patients with major **depressive** disorder.
AUTHOR: Brannan Stephen K; Mallinckrodt Craig H; Brown Eileen B; Wohlreich Madelaine M; Watkin John G; Schatzberg Alan F
CORPORATE SOURCE: Cyberonics, Houston, TX 77058, USA.
SOURCE: Journal of psychiatric research, (2005 Jan) 39 (1) 43-53.
Journal code: 0376331. ISSN: 0022-3956.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(MULTICENTER STUDY)
(RANDOMIZED CONTROLLED TRIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200504
ENTRY DATE: Entered STN: 20041027
Last Updated on STN: 20050413
Entered Medline: 20050412

AB BACKGROUND: While emotional symptoms such as **depressed** mood and loss of interest have traditionally been considered to constitute the core symptoms of major **depressive** disorder (MDD), the prevalence and importance of **painful** physical symptoms such as back **pain**, abdominal **pain**, and musculoskeletal **pain** is becoming increasingly appreciated. **Antidepressants** possessing dual **serotonin/norepinephrine** (5-HT/NE) **reuptake inhibition** may demonstrate greater efficacy in the alleviation of **pain**. The efficacy of duloxetine, a balanced and potent dual **reuptake inhibitor** of 5-HT and NE, was evaluated within a cohort of **depressed** patients with associated **painful** physical symptoms. METHODS: In this multicenter, double-blind, placebo-controlled study, patients meeting DSM-IV criteria for MDD were randomized to receive placebo (N=141) or duloxetine 60 mg QD (N=141). Patients were required to have a 17-item Hamilton Rating Scale for **Depression** (HAMD17) total score ≥ 15 , a Clinical Global Impression of Severity (CGI-S) score ≥ 4 , and a Brief **Pain** Inventory (BPI) Average **Pain** score ≥ 2 at baseline. The primary efficacy measure was the BPI Average **Pain** score, while secondary measures included other BPI items, the HAMD17 total score, CGI-S, the Patient Global Impression of Improvement (PGI-I) scale, Visual Analog Scales (VAS) for **pain**, and the Symptom Questionnaire, Somatic Subscale (SQSS). Safety was evaluated by recording treatment-emergent adverse events (spontaneously reported), vital signs, and laboratory analytes. RESULTS: Mean changes in BPI Average **Pain** for duloxetine- and placebo-treated patients differed significantly at most visits, but only approached significance at endpoint $p=0.066$. For the main effect of treatment (pooling all visits), significant advantages for duloxetine-treated patients were found in 10 of 11 assessed BPI **pain** severity and **pain** interference items, in addition to VAS overall **pain** and back **pain**. Mean changes in **pain** measures for duloxetine-treated patients corresponded to improvements of 25-50%, compared with 19-39% for placebo. Mean changes at endpoint in **depression** rating scales (HAMD17, CGI-S, PGI-I) did not differ significantly between duloxetine and placebo treatment groups due to unusually high placebo response. The magnitude of placebo treatment effects (as measured by HAMD17 total score and Maier subscale) was significantly smaller in patients with 1 previous **depressive** episode, compared to those patients with no previous episodes. In

patients with 1 previous **depressive** episode the advantage of duloxetine over placebo was similar to previous studies. Rates of discontinuation due to adverse events were 14.2% vs. 2.1% for duloxetine and placebo, respectively $p < 0.001$. Treatment-emergent adverse events reported at a significantly higher rate by duloxetine-treated patients included nausea, dry mouth, fatigue, and decreased appetite. **CONCLUSIONS:** In this study, duloxetine (60 mg QD) was shown to be an effective treatment for the **painful** physical symptoms which are frequently associated with **depression**. Improvements in **pain** severity occurred independently of changes in **depressive** symptom severity.

CT Check Tags: Female; Male
Administration, Oral
Adult

*Antidepressive Agents: AD, administration & dosage
Antidepressive Agents: AE, adverse effects
*Antidepressive Agents: TU, therapeutic use
*Depressive Disorder, Major: CO, complications
*Depressive Disorder, Major: DT, drug therapy

Double-Blind Method

Drug Administration Schedule

Humans

Middle Aged

*Pain: DT, drug therapy

*Pain: ET, etiology

Placebos

Research Support, Non-U.S. Gov't

Severity of Illness Index

*Thiophenes: AD, administration & dosage

Thiophenes: AE, adverse effects

*Thiophenes: TU, therapeutic use

Treatment Outcome

RN 116539-58-3 (duloxetine)

CN 0 (**Antidepressive** Agents); 0 (Placebos); 0 (Thiophenes)

L91 ANSWER 7 OF 313

MEDLINE on STN

DUPLICATE 9

ACCESSION NUMBER: 2005424039 MEDLINE

DOCUMENT NUMBER: PubMed ID: 16089245

TITLE: Duloxetine for management of stress urinary incontinence.

AUTHOR: Guay David R P

CORPORATE SOURCE: Department of Experimental and Clinical Pharmacology,
College of Pharmacy, University of Minnesota, Minneapolis
55455, USA.. guayx001@umn.edu

SOURCE: Am J Geriatr Pharmacother, (2005 Mar) 3 (1) 25-38. Ref: 45
Journal code: 101190325. ISSN: 1543-5946.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

General Review; (REVIEW)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200508

ENTRY DATE: Entered STN: 20050811

Last Updated on STN: 20050824

Entered Medline: 20050823

AB **OBJECTIVE:** The aim of this article was to review data regarding the efficacy and tolerability of duloxetine, a selective **serotonin** (5-HT)-**norepinephrine** (NE) **reuptake inhibitor** that has received US Food and Drug Administration marketing approval for the treatment of major **depressive** disorder and **painful**

diabetic neuropathy, and that has been investigated as a treatment for stress urinary incontinence. **METHODS:** A MEDLINE/PubMed search was conducted to identify English-language study reports. In addition, proceedings of meetings of the International Continence Society, European Association of Urology, American Urological Association, and American College of Obstetrics and Gynecology were reviewed for relevant abstracts (search terms included duloxetine, thiophenes, serotonin **uptake inhibitors**, adrenergic **uptake inhibitors**, and stress urinary incontinence). Additional references were obtained from the bibliographies of these sources. Data for the period from 1986 through January 2005 were reviewed. **RESULTS:** All in vitro and in vivo studies of duloxetine were included. Because both 5-HT and NE are involved in the maintenance of urinary continence, duloxetine may have a role in the treatment of urinary incontinence. Duloxetine is primarily eliminated via metabolism, with < 1% of the parent compound excreted via urine. Duloxetine QD or BID has been found to be significantly superior to placebo in reducing incontinence episode frequency ($P < 0.001$ to $P < 0.05$), increasing the interval between micturitions ($P < 0.001$ to $P = 0.004$), and improving the condition as measured by patient self-report ($P < 0.001$ to $P = 0.028$) and incontinence quality-of-life scores ($P = 0.002$ to $P = 0.03$). The most problematic adverse events are nausea, dry mouth, constipation, dizziness, and insomnia. **CONCLUSIONS:** Although statistically superior to placebo in efficacy trials, the clinical effects of duloxetine therapy on incontinence are small, suggesting that any benefits to the patient would be modest and must be weighed against the drug's adverse event profile. No comparative efficacy/tolerability data with alpha-receptor agonists (eg, pseudoephedrine) are available. On the basis of available data, duloxetine is a modest, but welcome, advance in the pharmacotherapeutic management of stress urinary incontinence.

CT **Adrenergic Uptake Inhibitors: AE, adverse effects**
Adrenergic Uptake Inhibitors: PK, pharmacokinetics
Adrenergic Uptake Inhibitors: PD, pharmacology
***Adrenergic Uptake Inhibitors: TU, therapeutic use**

Animals

Biotransformation

Clinical Trials

Drug Interactions

Humans

Rats

Thiophenes: AE, adverse effects

Thiophenes: PK, pharmacokinetics

Thiophenes: PD, pharmacology

*Thiophenes: TU, therapeutic use

*Urinary Incontinence, Stress: DT, drug therapy

RN 116539-58-3 (duloxetine)

CN 0 (Adrenergic **Uptake Inhibitors**); 0 (Thiophenes)

L91 ANSWER 8 OF 313 MEDLINE on STN DUPLICATE 13

ACCESSION NUMBER: 2004488145 MEDLINE

DOCUMENT NUMBER: PubMed ID: 15457467

TITLE: A double-blind, multicenter trial comparing duloxetine with placebo in the treatment of fibromyalgia patients with or without major **depressive** disorder.

AUTHOR: Arnold Lesley M; Lu Yili; Crofford Leslie J; Wohlreich Madelaine; Detke Michael J; Iyengar Smriti; Goldstein David J

CORPORATE SOURCE: University of Cincinnati College of Medicine, Cincinnati, Ohio 45219, USA.. Lesley.Arnold@uc.edu

SOURCE: Arthritis and rheumatism, (2004 Sep) 50 (9) 2974-84.

Journal code: 0370605. ISSN: 0004-3591.

PUB. COUNTRY: United States
DOCUMENT TYPE: (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(MULTICENTER STUDY)
(RANDOMIZED CONTROLLED TRIAL)

LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200410
ENTRY DATE: Entered STN: 20041001
Last Updated on STN: 20041027
Entered Medline: 20041026

AB OBJECTIVE: To assess the efficacy and safety of duloxetine, a **serotonin and norepinephrine reuptake inhibitor**, in subjects with primary fibromyalgia, with or without current major **depressive** disorder. METHODS: This study was a randomized, double-blind, placebo-controlled trial conducted in 18 outpatient research centers in the US. A total of 207 subjects meeting the American College of Rheumatology criteria for primary fibromyalgia were enrolled (89% female, 87% white, mean age 49 years, 38% with current major **depressive** disorder). After single-blind placebo treatment for 1 week, subjects were randomly assigned to receive duloxetine 60 mg twice a day (n = 104) or placebo (n = 103) for 12 weeks. Co-primary outcome measures were the Fibromyalgia Impact Questionnaire (FIQ) total score (score range 0-80, with 0 indicating no impact) and FIQ **pain** score (score range 0-10). Secondary outcome measures included mean tender point **pain** threshold, number of tender points, FIQ fatigue, tiredness on awakening, and stiffness scores, Clinical Global Impression of Severity (CGI-Severity) scale, Patient Global Impression of Improvement (PGI-Improvement) scale, Brief **Pain** Inventory (short form), Medical Outcomes Study Short Form 36, Quality of Life in **Depression** Scale, and Sheehan Disability Scale. RESULTS: Compared with placebo-treated subjects, duloxetine-treated subjects improved significantly more (P = 0.027) on the FIQ total score, with a treatment difference of -5.53 (95% confidence interval -10.43, -0.63), but not significantly more on the FIQ **pain** score (P = 0.130). Compared with placebo-treated subjects, duloxetine-treated subjects had significantly greater reductions in Brief **Pain** Inventory average **pain** severity score (P = 0.008), Brief **Pain** Inventory average interference from **pain** score (P = 0.004), number of tender points (P = 0.002), and FIQ stiffness score (P = 0.048), and had significantly greater improvement in mean tender point **pain** threshold (P = 0.002), CGI-Severity (P = 0.048), PGI-Improvement (P = 0.033), and several quality-of-life measures. Duloxetine treatment improved fibromyalgia symptoms and **pain** severity regardless of baseline status of major **depressive** disorder. Compared with placebo-treated female subjects (n = 92), duloxetine-treated female subjects (n = 92) demonstrated significantly greater improvement on most efficacy measures, while duloxetine-treated male subjects (n = 12) failed to improve significantly on any efficacy measure. The treatment effect on significant **pain** reduction in female subjects was independent of the effect on mood or anxiety. Duloxetine was safely administered and well tolerated. CONCLUSION: In this randomized, controlled, 12-week trial (with a 1-week placebo lead-in phase), duloxetine was an effective and safe treatment for many of the symptoms associated with fibromyalgia in subjects with or without major **depressive** disorder, particularly for women, who had significant improvement across most outcome measures.

CT Check Tags: Comparative Study; Female; Male

Comorbidity

*Depressive Disorder, Major: DT, drug therapy

Depressive Disorder, Major: EP, epidemiology

Double-Blind Method

*Fibromyalgia: DT, drug therapy

Fibromyalgia: EP, epidemiology

Humans

Middle Aged

*Neurotransmitter Uptake Inhibitors: TU, therapeutic use

Research Support, Non-U.S. Gov't

Sex Factors

*Thiophenes: TU, therapeutic use

Treatment Outcome

RN 116539-58-3 (duloxetine)

CN 0 (Neurotransmitter Uptake Inhibitors); 0 (Thiophenes)

L91 ANSWER 9 OF 313 MEDLINE on STN DUPLICATE 14

ACCESSION NUMBER: 2004264085 MEDLINE

DOCUMENT NUMBER: PubMed ID: 15162896

TITLE: Treatment of **pain** syndromes with venlafaxine.

AUTHOR: Grothe Dale R; Scheckner Brian; Albano Dominick

CORPORATE SOURCE: Global Medical Communications, Neuroscience, Wyeth Pharmaceuticals, Collegeville, Pennsylvania 19426, USA.

SOURCE: Pharmacotherapy, (2004 May) 24 (5) 621-9. Ref: 59
Journal code: 8111305. ISSN: 0277-0008.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200408

ENTRY DATE: Entered STN: 20040528
Last Updated on STN: 20040818
Entered Medline: 20040817

AB Major **depressive** disorder (MDD) and anxiety disorders such as generalized anxiety disorder (GAD) are often accompanied by chronic **painful** symptoms. Examples of such symptoms are backache, headache, gastrointestinal **pain**, and joint **pain**. In addition, **pain** generally not associated with major **depression** or an anxiety disorder, such as peripheral neuropathic **pain** (e.g., diabetic neuropathy and postherpetic neuralgia), cancer **pain**, and fibromyalgia, can be challenging for primary care providers to treat. **Antidepressants** that block reuptake of both **serotonin** and **norepinephrine**, such as the tricyclic **antidepressants** (e.g., amitriptyline), have been used to treat **pain** syndromes in patients with or without comorbid MDD or GAD. Venlafaxine, a **serotonin** and **norepinephrine** **reuptake inhibitor**, has been safe and effective in animal models, healthy human volunteers, and patients for treatment of various **pain** syndromes. The use of venlafaxine for treatment of **pain** associated with MDD or GAD, neuropathic **pain**, headache, fibromyalgia, and postmastectomy **pain** syndrome is reviewed. Currently, no **antidepressants**, including venlafaxine, are approved for the treatment of chronic **pain** syndromes. Additional randomized, controlled trials are necessary to fully elucidate the role of venlafaxine in the treatment of chronic **pain**.

CT Analgesics: AE, adverse effects
*Analgesics: TU, therapeutic use

Animals

*Anxiety Disorders: CO, complications

Anxiety Disorders: PP, physiopathology

Cyclohexanols: AE, adverse effects

*Cyclohexanols: TU, therapeutic use

*Depressive Disorder, Major: CO, complications

Depressive Disorder, Major: PP, physiopathology

Humans

*Pain

Pain: DT, drug therapy

Pain: ET, etiology

Pain: PP, physiopathology

Pain, Postoperative: DT, drug therapy

Randomized Controlled Trials

RN 93413-69-5 (venlafaxine)

CN 0 (Analgesics); 0 (Cyclohexanols)

L91 ANSWER 10 OF 313 MEDLINE on STN DUPLICATE 15
 ACCESSION NUMBER: 2004619620 MEDLINE
 DOCUMENT NUMBER: PubMed ID: 15589385
 TITLE: Duloxetine in the acute and long-term treatment of major
 depressive disorder: a placebo- and
 paroxetine-controlled trial.
 AUTHOR: Detke Michael J; Wiltse Curtis G; Mallinckrodt Craig H;
 McNamara Robert K; Demitrack Mark A; Bitter Istvan
 CORPORATE SOURCE: Lilly Research Laboratories, Eli Lilly and Company, Lilly
 Corporate Center, Indianapolis, IN 46285, USA..
 DETKE_MICHAEL@LILLY.COM
 SOURCE: European neuropsychopharmacology : journal of the European
 College of Neuropsychopharmacology, (2004 Dec) 14 (6)
 457-70.
 Journal code: 9111390. ISSN: 0924-977X.
 PUB. COUNTRY: Netherlands
 DOCUMENT TYPE: (CLINICAL TRIAL)
 Journal; Article; (JOURNAL ARTICLE)
 (RANDOMIZED CONTROLLED TRIAL)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 200501
 ENTRY DATE: Entered STN: 20041220
 Last Updated on STN: 20050114
 Entered Medline: 20050113

AB BACKGROUND: Duloxetine is a balanced and potent dual reuptake
 inhibitor of serotonin (5-HT) and norepinephrine
 (NE) that has previously been shown to be effective in the acute treatment
 of major depressive disorder (MDD). This placebo-controlled
 study assesses the safety and efficacy of duloxetine (80 or 120 mg/day)
 and paroxetine (20 mg QD) during an initial 8-week acute phase and
 subsequent 6-month continuation phase treatment of MDD. METHOD: In this
 randomized, double-blind, placebo-controlled trial, adult outpatients (age
 >or= 18 years) meeting DSM-IV criteria for MDD received placebo (n = 93),
 duloxetine 80 mg/day (40 mg BID; n = 95), duloxetine 120 mg/day (60 mg
 BID; n = 93), or paroxetine (20 mg QD; n = 86) for 8 weeks. Patients who
 had a >or= 30% reduction from baseline in HAMD(17) total score during the
 acute phase were allowed to continue on the same (blinded) treatment for a
 6-month continuation phase. Efficacy measures included the 17-item
 Hamilton Rating Scale for Depression (HAMD(17)) total score,
 HAMD(17) subscales, the Montgomery-Asberg Depression Rating
 Scale (MADRS), the Hamilton Anxiety Rating Scale (HAMA), Visual Analog

Scales (VAS) for **pain**, the Clinical Global Impression of Severity (CGI-S) and Patient Global Impression of Improvement (PGI-I) scales, the 28-item Somatic Symptom Inventory (SSI), and the Sheehan Disability Scale (SDS). Safety and tolerability were assessed using treatment-emergent adverse events, discontinuations due to adverse events, vital signs, ECGs, laboratory tests, and the Arizona Sexual Experiences Scale (ASEX). RESULTS: During the acute phase, patients receiving duloxetine 80 mg/day, duloxetine 120 mg/day, or paroxetine 20 mg QD had significantly greater reductions in HAMD(17) total score compared with placebo. Both duloxetine (80 and 120 mg/day) and paroxetine treatment groups had significantly greater improvement, compared with placebo, in MADRS, HAMA, CGI-S, and PGI-I scales. Estimated probabilities of remission at week 8 for patients receiving duloxetine 80 mg/day (51%), duloxetine 120 mg/day (58%), and paroxetine (47%) were significantly greater compared with those receiving placebo (30%). The rate of discontinuation due to adverse events among duloxetine-treated patients (80 and 120 mg/day) did not differ significantly from the rate in the placebo group. Treatment-emergent adverse events reported significantly more frequently by duloxetine-treated patients than by patients receiving placebo were constipation (80 and 120 mg/day), increased sweating (120 mg/day), and somnolence (120 mg/day). The incidence of acute treatment-emergent sexual dysfunction in duloxetine- and paroxetine-treated patients was 46.5% and 62.8%, respectively. During the 6-month continuation phase, duloxetine (80 and 120 mg/day) and paroxetine treatment groups demonstrated significant improvement in HAMD(17) total score. Treatment-emergent adverse events occurring most frequently in each active treatment group during the continuation phase were viral infection (duloxetine 80 mg/day), diarrhea (duloxetine 120 mg/day), and headache (paroxetine 20 mg QD). CONCLUSION: These data support previous findings that duloxetine is safe, efficacious, and well tolerated in the acute treatment of MDD. Furthermore, these data provide the first demonstration under double-blind, placebo-controlled conditions that the efficacy and tolerability of duloxetine are maintained during chronic treatment.

CT Check Tags: Comparative Study; Female; Male
Adult

Antidepressive Agents, Second-Generation: AE, adverse effects
***Antidepressive Agents, Second-Generation: TU, therapeutic use**
 Body Weight: DE, drug effects
 Cardiovascular Diseases: CI, chemically induced
 Cardiovascular Diseases: EP, epidemiology
***Depressive Disorder, Major: DT, drug therapy**
Depressive Disorder, Major: PX, psychology
 Dose-Response Relationship, Drug
 Double-Blind Method
 Electrocardiography: DE, drug effects
 Hemodynamic Processes: DE, drug effects
 Humans
 Longitudinal Studies
 Middle Aged
 Paroxetine: AE, adverse effects
***Paroxetine: TU, therapeutic use**
 Psychiatric Status Rating Scales
 Research Support, Non-U.S. Gov't
 Sex Disorders: CI, chemically induced
 Sex Disorders: EP, epidemiology
 Thiophenes: AE, adverse effects
***Thiophenes: TU, therapeutic use**

RN 116539-58-3 (duloxetine); 61869-08-7 (Paroxetine)

CN 0 (Antidepressive Agents, Second-Generation); 0 (Thiophenes)

L91 ANSWER 11 OF 313 MEDLINE on STN DUPLICATE 16
ACCESSION NUMBER: 2004379528 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15232330
TITLE: Duloxetine in the treatment of **depression**: a
double-blind placebo-controlled comparison with paroxetine.
AUTHOR: Goldstein David J; Lu Yili; Detke Michael J; Wiltse Curtis;
Mallinckrodt Craig; Demitrack Mark A
CORPORATE SOURCE: PRN Consulting, Indianapolis, IN, USA.
SOURCE: Journal of clinical psychopharmacology, (2004 Aug) 24 (4)
389-99.
Journal code: 8109496. ISSN: 0271-0749.
PUB. COUNTRY: United States
DOCUMENT TYPE: (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(MULTICENTER STUDY)
(RANDOMIZED CONTROLLED TRIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200411
ENTRY DATE: Entered STN: 20040801
Last Updated on STN: 20041105
Entered Medline: 20041104

AB CONTEXT: Major **depressive** disorder causes significant morbidity
and mortality. Current therapies fail to fully treat both emotional and
physical symptoms of major **depressive** disorder. OBJECTIVE: To
evaluate duloxetine, a dual **reuptake inhibitor** of
serotonin and **norepinephrine**, on improvement of
emotional and **painful** physical symptoms. DESIGN: Randomized,
double-blind, evaluation of duloxetine at 40 mg/d (20 mg twice daily) and
80 mg/d (40 mg twice daily) versus placebo and paroxetine 20 mg/d in
depressed outpatients. MAIN OUTCOME MEASURES: The primary
efficacy measure was the 17-item Hamilton **Depression** Rating
Scale. Visual Analog Scales for **pain**, Clinical Global
Impression of Severity, Patient's Global Impression of Improvement, and
Quality of Life in **Depression** Scale were also used. Safety was
evaluated by assessing discontinuation rates, adverse event rates, vital
signs, and laboratory tests. RESULTS: Duloxetine 80 mg/d was superior to
placebo on mean 17-item Hamilton **Depression** Rating Scale total
change by 3.62 points (95% CI 1.38, 5.86; P = 0.002). Duloxetine at 40
mg/d was also significantly superior to placebo by 2.43 points (95% CI
0.19, 4.66; P = 0.034), while paroxetine was not (1.51 points; 95% CI
-0.55, 3.56; P = 0.150). Duloxetine 80 mg/d was superior to placebo for
most other measures, including overall **pain** severity, and was
superior to paroxetine on 17-item Hamilton **Depression** Rating
Scale improvement (by 2.39 points; 95% CI 0.14, 4.65; P = 0.037) and
estimated probability of remission (57% for duloxetine 80 mg/d, 34% for
paroxetine; P = 0.022). The only adverse event reported significantly
more frequently for duloxetine 80 mg/d than for paroxetine was insomnia
(19.8% for duloxetine 80 mg/d, 8.0% for paroxetine; P = 0.031).
Hypertension incidence was not affected by any treatment. CONCLUSION:
Duloxetine therapy was efficacious for emotional and physical symptoms of
depression, with a selective serotonin **reuptake**
inhibitor-like profile of side effects.
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CT Check Tags: Comparative Study; Female; Male
Adult
Analysis of Variance

Confidence Intervals

Depressive Disorder, Major: DI, diagnosis

*Depressive Disorder, Major: DT, drug therapy

Depressive Disorder, Major: PX, psychology

Diagnostic and Statistical Manual of Mental Disorders

Dose-Response Relationship, Drug

Double-Blind Method

Humans

Logistic Models

Middle Aged

Paroxetine: AE, adverse effects

*Paroxetine: TU, therapeutic use

Research Support, Non-U.S. Gov't

Sleep Initiation and Maintenance Disorders: CI, chemically induced

Sleep Initiation and Maintenance Disorders: PX, psychology

Thiophenes: AE, adverse effects

*Thiophenes: TU, therapeutic use

RN 116539-58-3 (duloxetine); 61869-08-7 (Paroxetine)

CN 0 (Thiophenes)

L91 ANSWER 12 OF 313 MEDLINE on STN DUPLICATE 17

ACCESSION NUMBER: 2004013101 MEDLINE

DOCUMENT NUMBER: PubMed ID: 14709757

TITLE: Effects of duloxetine on **painful** physical symptoms associated with **depression**.

AUTHOR: Goldstein David J; Lu Yili; Detke Michael J; Hudson James; Iyengar Smriti; Demitrack Mark A

CORPORATE SOURCE: Department of Psychiatry and the Department of Pharmacology and toxicology, Indiana University School of Medicine, Indianapolis, USA.. DJGoldstein@consultPRNC.com

SOURCE: Psychosomatics, (2004 Jan-Feb) 45 (1) 17-28. .
Journal code: 0376506. ISSN: 0033-3182.

PUB. COUNTRY: United States

DOCUMENT TYPE: (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(MULTICENTER STUDY)
(RANDOMIZED CONTROLLED TRIAL)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200402

ENTRY DATE: Entered STN: 20040108
Last Updated on STN: 20040213
Entered Medline: 20040212

AB **Painful** physical symptoms are common features of major **depressive** disorder and may be the presenting complaints in primary care settings. The effect of the dual **serotonin** (5-HT) and **norepinephrine reuptake inhibitor** duloxetine on emotional and **painful** physical symptoms in outpatients with major **depressive** disorder was evaluated in three randomized, double-blind, placebo-controlled trials. The trials' primary objective was to evaluate the effect of duloxetine on mood, and subjects were not enrolled on the basis of presence, type, or severity of **pain**. However, the **pain**-relieving effects of duloxetine were evaluated by a priori defined analyses of results from a visual analogue scale and the Somatic Symptom Inventory. Compared with placebo, duloxetine was associated with significant reduction in **pain** severity. The authors concluded that duloxetine reduces the **painful** physical symptoms of **depression**.

CT Check Tags: Female; Male

*Adrenergic Uptake Inhibitors: TU, therapeutic use

Adult

*Antidepressive Agents: TU, therapeutic use

*Depressive Disorder: DT, drug therapy

Depressive Disorder: PP, physiopathology

Depressive Disorder: PX, psychology

Dose-Response Relationship, Drug

Double-Blind Method

Humans

Norepinephrine: ME, metabolism

*Pain: DT, drug therapy

Pain: PP, physiopathology

Pain Measurement

Research Support, Non-U.S. Gov't

Serotonin: ME, metabolism

*Serotonin Uptake Inhibitors: TU, therapeutic use

*Thiophenes: TU, therapeutic use

Treatment Outcome

RN 116539-58-3 (duloxetine); 50-67-9 (Serotonin); 51-41-2 (Norepinephrine)

CN 0 (Adrenergic Uptake Inhibitors); 0 (Antidepressive Agents); 0 (Serotonin Uptake Inhibitors); 0 (Thiophenes)

L91 ANSWER 13 OF 313 MEDLINE on STN DUPLICATE 21
 ACCESSION NUMBER: 2003488516 MEDLINE
 DOCUMENT NUMBER: PubMed ID: 14565792
 TITLE: Venlafaxine treatment of fibromyalgia.
 AUTHOR: Sayar Kemal; Aksu Gokhan; Ak Ismail; Tosun Mehmet
 CORPORATE SOURCE: Karadeniz Technical University School of Medicine, Farabi Hospital, Trabzon, Turkey.. mkemalsayar@superonline.com
 SOURCE: Annals of pharmacotherapy, (2003 Nov) 37 (11) 1561-5.
 Journal code: 9203131. ISSN: 1060-0280.
 PUB. COUNTRY: United States
 DOCUMENT TYPE: (CLINICAL TRIAL)
 Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 200403
 ENTRY DATE: Entered STN: 20031021
 Last Updated on STN: 20040306
 Entered Medline: 20040305

AB BACKGROUND: Although the pathophysiology of fibromyalgia is unknown, central monoaminergic transmission may play a role. **Antidepressants** have proved to be successful in alleviating symptoms of fibromyalgia. Medications that act on multiple neurotransmitters may be more effective in symptom management. **OBJECTIVE:** To assess the efficacy of venlafaxine, a potent inhibitor of both **norepinephrine** and **serotonin** reuptake, in the treatment of patients with fibromyalgia. **METHODS:** Fifteen patients with fibromyalgia were assessed prior to and after treatment with fixed-dose venlafaxine 75 mg/d. Before initiation of pharmacotherapy, patients were interviewed with the Structured Clinical Interview for Axis I disorders in the Diagnostic and Statistical Manual of Mental Disorders, 4th edition. The study lasted for 12 weeks, and patients were evaluated in weeks 6 and 12. The primary outcome measures were the Fibromyalgia Impact Questionnaire (FIQ) total score and **pain** score. The anxiety and **depression** levels of the patients were measured with the Beck **Depression**, the Beck Anxiety, the Hamilton Anxiety, and the Hamilton **Depression** scales. **RESULTS:** There was a significant

improvement in the mean intensity of **pain** ($F = 14.3$; $p = 0.0001$) and in the disability caused by fibromyalgia ($F = 42.7$; $p = 0.0001$) from baseline to week 12 of treatment. The **depression** and anxiety scores also decreased significantly from baseline to week 12. The improvement in the FIQ scores did not correlate with the decrease of scores in both patient- and physician-rated **depression** and anxiety inventories. Change in **pain** scores also was not correlated with the change in **depression** and anxiety scores. CONCLUSIONS: Venlafaxine was quite promising in alleviating the **pain** and disability associated with fibromyalgia. This effect seems to be independent of its anxiolytic and **antidepressant** properties. Blockade of both **norepinephrine** and **serotonin** reuptake might be more effective than blockade of either neurotransmitter alone in the treatment of fibromyalgia.

CT Check Tags: Female

*Adrenergic Uptake Inhibitors: TU, therapeutic use

Adult

Anxiety: CO, complications

Anxiety: DT, drug therapy

*Cyclohexanols: TU, therapeutic use

Depression: CO, complications

Depression: DT, drug therapy

Fibromyalgia: CO, complications

*Fibromyalgia: DT, drug therapy

Humans

Pain: DT, drug therapy

Pain: ET, etiology

*Serotonin Uptake Inhibitors: TU, therapeutic use

RN 93413-69-5 (venlafaxine)

CN 0 (Adrenergic Uptake Inhibitors); 0 (Cyclohexanols); 0 (Serotonin Uptake Inhibitors)

L91 ANSWER 14 OF 313 MEDLINE on STN DUPLICATE 22
 ACCESSION NUMBER: 2003422684 MEDLINE
 DOCUMENT NUMBER: PubMed ID: 12964171
 TITLE: Duloxetine in treatment of anxiety symptoms associated with **depression**.
 AUTHOR: Dunner David L; Goldstein David J; Mallinckrodt Craig; Lu Yili; Detke Michael J
 CORPORATE SOURCE: Department of Psychiatry and Behavioral Sciences, University of Washington Center for Anxiety and Depression, Seattle, WA, USA.
 SOURCE: Depression and anxiety, (2003) 18 (2) 53-61. Journal code: 9708816. ISSN: 1091-4269.
 PUB. COUNTRY: United States
 DOCUMENT TYPE: (CLINICAL TRIAL)
 Journal; Article; (JOURNAL ARTICLE)
 (RANDOMIZED CONTROLLED TRIAL)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 200402
 ENTRY DATE: Entered STN: 20030910
 Last Updated on STN: 20040213
 Entered Medline: 20040212
 AB Most patients with major **depressive** disorder (MDD) have symptoms of anxiety associated with their **depression**. Duloxetine, a potent and balanced dual **serotonin** and **norepinephrine** reuptake inhibitor, is effective in the treatment of **depression**. We investigated its effects in treating the symptoms

of anxiety in **depressed** patients. This investigation includes all the placebo-controlled studies of duloxetine in MDD but focuses on four trials in which duloxetine was superior to placebo on the primary outcome measure of the 17-item Hamilton **Depression** Rating Scale (HAMD(17)) total score. Studies 1 and 2 included duloxetine at 60 mg/d (the recommended starting and therapeutic dose) and placebo. Study 3 included duloxetine 120 mg/d (administered as 60 mg b.i.d.), fluoxetine 20 mg/d, and placebo. Study 4 included duloxetine 40 mg/d (administered as 20 mg b.i.d.), duloxetine 80 mg/d (administered as 40 mg b.i.d.), paroxetine 20 mg/d, and placebo. Anxiety was assessed in all studies using the HAMD anxiety/somatization subfactor and the anxiety-psychic item (HAMD Item 10). Studies 3 and 4 also included the Hamilton Anxiety Rating Scale (HAMA). Across the four studies, duloxetine at doses of ≥ 60 mg was compared with placebo on 10 outcomes and with either paroxetine or fluoxetine on 6 outcomes. In 8 comparisons, mean improvement for duloxetine was significantly greater than placebo at the last study visit and/or across all study visits. In 3 comparisons, the mean improvement for duloxetine was significantly greater than paroxetine or fluoxetine. In these studies, duloxetine provided rapid relief of anxiety symptoms associated with **depression**. Previous reports have summarized duloxetine's efficacy in treating the core emotional symptoms and **painful** physical symptoms associated with **depression**. Duloxetine's efficacy in treating a broad spectrum of symptoms associated with **depression**, including mood, anxiety, and **painful** physical symptoms, may be attributed to dual **reuptake inhibition** of both **serotonin** and **norepinephrine**. Efficacy in these three key symptom domains may in turn explain the high probabilities of remission (43-57%) observed in these studies. Copyright 2003 Wiley-Liss, Inc.

CT Check Tags: Female; Male

Adult

Antidepressive Agents: AD, administration & dosage

***Antidepressive Agents: TU, therapeutic use**

Anxiety: DI, diagnosis

*Anxiety: DT, drug therapy

*Anxiety: ET, etiology

Depression: DI, diagnosis

***Depression: PX, psychology**

Diagnostic and Statistical Manual of Mental Disorders

Double-Blind Method

Drug Administration Schedule

Humans

Questionnaires

Research Support, Non-U.S. Gov't

Severity of Illness Index

Thiophenes: AD, administration & dosage

*Thiophenes: TU, therapeutic use

RN 116539-58-3 (duloxetine)

CN 0 (**Antidepressive Agents**); 0 (Thiophenes)

L91 ANSWER 15 OF 313 MEDLINE on STN DUPLICATE 23

ACCESSION NUMBER: 2003112553 MEDLINE

DOCUMENT NUMBER: PubMed ID: 12625027

TITLE: New hope in the treatment of **painful** symptoms in **depression**.

AUTHOR: Briley Mike

CORPORATE SOURCE: NeuroBiz Consulting and Communications Les Grezes La Verdarie 81100 Castres, France.. mike.briley@neurobiz.com

SOURCE: Current opinion in investigational drugs (London, England :

2000), (2003 Jan) 4 (1) 42-5. Ref: 42
 Journal code: 100965718. ISSN: 1472-4472.

PUB. COUNTRY: England: United Kingdom
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
 General Review; (REVIEW)
 (REVIEW, TUTORIAL)

LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 200310
 ENTRY DATE: Entered STN: 20030311
 Last Updated on STN: 20031011
 Entered Medline: 20031010

AB **Depression** is increasingly seen as a triad of psychological, somatic and physical symptoms that all need to be treated to achieve maximal remission. In primary care, physical symptoms such as **pain**, are the principal presenting symptoms, and a common psychopharmacology between **pain** and **depression** suggests that compounds that **inhibit** the **reuptake** of both **serotonin** and **norepinephrine** are likely to produce the greatest relief from **depression** and chronic **pain**. Recent, principally open, trials with members of the new selective **serotonin** and **norepinephrine reuptake inhibitor** class of **antidepressants** such as venlafaxine, milnacipran and duloxetine (Eli Lilly & Co/Shionogi & Co Ltd), suggest that these compounds may be effective in relieving **pain** both associated with, and independent of **depression**

CT Animals
 ***Antidepressive Agents: TU, therapeutic use**
 Clinical Trials
 Cyclohexanols: TU, therapeutic use
 Cyclopropanes: TU, therapeutic use
 ***Depressive Disorder: CO, complications**
 Humans
 ***Pain: DT, drug therapy**
 ***Pain: ET, etiology**
 Thiophenes: TU, therapeutic use

RN 116539-58-3 (duloxetine); 92623-85-3 (milnacipran); 93413-69-5 (venlafaxine)

CN 0 (**Antidepressive Agents**); 0 (Cyclohexanols); 0 (Cyclopropanes); 0 (Thiophenes)

L91 ANSWER 16 OF 313 MEDLINE on STN DUPLICATE 24
 ACCESSION NUMBER: 2003477724 MEDLINE
 DOCUMENT NUMBER: PubMed ID: 14552654
 TITLE: Efficacy and tolerability of duloxetine, a novel dual **reuptake inhibitor**, in the treatment of major **depressive** disorder.
 AUTHOR: Schatzberg Alan F
 CORPORATE SOURCE: Department of Psychiatry, Stanford University School of Medicine, Stanford, CA 94305-5717, USA..
 afschatz@stanford.edu
 SOURCE: Journal of clinical psychiatry, (2003) 64 Suppl 13 30-7.
 Ref: 45
 Journal code: 7801243. ISSN: 0160-6689.

PUB. COUNTRY: United States
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
 General Review; (REVIEW)
 (REVIEW, TUTORIAL)

LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200401
ENTRY DATE: Entered STN: 20031015
Last Updated on STN: 20040121
Entered Medline: 20040120

AB Although highly selective **antidepressants** such as the selective serotonin **reuptake inhibitors** represent an advance over older drugs with respect to tolerability, they are not more effective than previous agents. **Antidepressants** that enhance transmission in more than one monoamine system may have greater efficacy than highly selective drugs, while equaling or improving their adverse effect profiles. This article reviews the properties of duloxetine, a potent and balanced inhibitor of **norepinephrine** and **serotonin** reuptake. Controlled studies indicate a high degree of efficacy, tolerability, and safety for duloxetine in the treatment of major **depressive** disorder. In particular, rapid therapeutic onset and high remission rates have been noted. Duloxetine appears to have significant benefit in the treatment of the **painful** physical symptoms associated with **depression**. The continued presence of such symptoms may predict relapse. Accordingly, it is hoped that duloxetine therapy may reduce the likelihood of **depressive** relapse.

CT **Adrenergic Uptake Inhibitors: AE, adverse effects**
Adrenergic Uptake Inhibitors: PD, pharmacology
***Adrenergic Uptake Inhibitors: TU, therapeutic use**
Clinical Trials

Depressive Disorder: DI, diagnosis
***Depressive Disorder: DT, drug therapy**
Depressive Disorder: PX, psychology

Humans

Multicenter Studies

Norepinephrine: ME, metabolism

Pain: DT, drug therapy

Research Support, Non-U.S. Gov't

Serotonin: ME, metabolism

Serotonin Uptake Inhibitors: AE, adverse effects

Serotonin Uptake Inhibitors: PD, pharmacology

***Serotonin Uptake Inhibitors: TU, therapeutic use**

Somatoform Disorders: DT, drug therapy

Thiophenes: AE, adverse effects

Thiophenes: PD, pharmacology

***Thiophenes: TU, therapeutic use**

Treatment Outcome

RN 116539-58-3 (duloxetine); 50-67-9 (Serotonin); 51-41-2 (Norepinephrine)

CN 0 (**Adrenergic Uptake Inhibitors**); 0 (Serotonin
Uptake Inhibitors); 0 (Thiophenes)

L91 ANSWER 17 OF 313 MEDLINE on STN DUPLICATE 25

ACCESSION NUMBER: 2003233984 MEDLINE

DOCUMENT NUMBER: PubMed ID: 12755646

TITLE: Physical symptoms of **depression**: unmet needs.

AUTHOR: Greden John F

CORPORATE SOURCE: Department of Psychiatry and University of Michigan
Depression Center, Ann Arbor, MI 48109, USA..
gredenj@umich.edu

SOURCE: Journal of clinical psychiatry, (2003) 64 Suppl 7 5-11.

Ref: 31

Journal code: 7801243. ISSN: 0160-6689.

PUB. COUNTRY: United States
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
 General Review; (REVIEW)
 (REVIEW, TUTORIAL)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 200307
 ENTRY DATE: Entered STN: 20030521
 Last Updated on STN: 20030702
 Entered Medline: 20030701

AB The burden of **depression** on society is sizable. Innate to this burden are underdiagnosis and under-treatment of unipolar and bipolar major **depressive** disorder in all parts of the health care system in part due to underrecognition of the physical symptoms that commonly are core components of major **depressive** disorder. Physical **pains** especially complicate the diagnosis of **depression**. Many patients de-emphasize psychosocial symptoms while emphasizing **pains** as their primary or sole complaints. There is a high correlation between the number of physical symptoms reported and the presence of **depression**. Additionally, patients with residual physical and emotional symptoms following treatment for **depression** appear to be at higher risk of relapse compared with those who have no residual symptoms. Complex genetic vulnerabilities underlie the **depressive** diathesis, and stress appears to be an accentuation for the gene expression that sets off episodes of **depression** in persons with these predispositions. If underdiagnosis interferes and acute treatment is not implemented early and effectively for initial episodes of **depression** and maintained after remission, individuals with genetic vulnerabilities may experience a pattern of recurrences, cycle acceleration, and increased severity. **Serotonin** and **norepinephrine** may be shared neurochemical links that tie **depression** and physical symptoms together. Thus, it is reasonable to hypothesize that **antidepressants** that incorporate both **serotonin** and **norepinephrine reuptake inhibition** might be a more efficacious treatment approach for patients with physical symptoms of **depression**.

CT Check Tags: Comparative Study; Female; Male
 Adolescent
 Adrenergic Uptake Inhibitors: TU, therapeutic use
 Adult
 Comorbidity
 Cost of Illness
 *Delivery of Health Care
 *Depressive Disorder: DI, diagnosis
 Depressive Disorder: DT, drug therapy
 Depressive Disorder: EP, epidemiology
 Health Care Costs
 Humans
 Norepinephrine
 Pain: DI, diagnosis
 Pain: EP, epidemiology
 Primary Health Care: ST, standards
 Recurrence
 Serotonin Uptake Inhibitors: TU, therapeutic use
 Treatment Outcome
 RN 51-41-2 (Norepinephrine)
 CN 0 (Adrenergic Uptake Inhibitors); 0 (Serotonin Uptake Inhibitors)

L91 ANSWER 18 OF 313 MEDLINE on STN DUPLICATE 27
ACCESSION NUMBER: 2002259687 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12000204
TITLE: Duloxetine, 60 mg once daily, for major **depressive**
disorder: a randomized double-blind placebo-controlled
trial.
COMMENT: Comment in: J Clin Psychiatry. 2002 Apr;63(4):305-7. PubMed
ID: 12000203
Comment in: J Clin Psychiatry. 2003 Jan;64(1):96; author
reply 96-7. PubMed ID: 12590632
AUTHOR: Detke Michael J; Lu Yili; Goldstein David J; Hayes John R;
Demitrack Mark A
CORPORATE SOURCE: Lilly Research Laboratories, Eli Lilly and Company,
Indianapolis, Ind 46285, USA.. detke_michael@lilly.com
SOURCE: Journal of clinical psychiatry, (2002 Apr) 63 (4) 308-15.
Journal code: 7801243. ISSN: 0160-6689.
PUB. COUNTRY: United States
DOCUMENT TYPE: (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(MULTICENTER STUDY)
(RANDOMIZED CONTROLLED TRIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200205
ENTRY DATE: Entered STN: 20020510
Last Updated on STN: 20030306
Entered Medline: 20020531
AB BACKGROUND: Despite treatment advances, major **depressive**
disorder (MDD) is still a significant cause of morbidity and mortality.
Current therapies frequently fall short of providing full remission. In
addition, physical symptoms are commonly seen in MDD patients, increasing
overall morbidity and health care utilization. Duloxetine hydrochloride,
a dual **reuptake inhibitor** of **serotonin** and
norepinephrine, was evaluated for efficacy and tolerability/safety
in the treatment of MDD and associated physical symptoms. METHOD: In this
multicenter, double-blind, parallel-group study, adult patients with
DSM-IV MDD were randomly assigned to receive placebo (N = 122) or
duloxetine (60 mg/day, N = 123) for 9 weeks. The primary efficacy measure
was the 17-item Hamilton Rating Scale for **Depression** (HAM-D-17)
total score. **Painful** physical symptoms were assessed using
visual analog scales, and global illness and quality of life were
evaluated using the Clinical Global Impressions-Severity scale, the
Patient Global Impressions-Improvement scale, and the Quality of Life in
Depression Scale. Safety and tolerability were determined by
monitoring discontinuation rates, adverse events, vital signs, and
laboratory results. RESULTS: Duloxetine was significantly superior to
placebo ($p < .001$) in reducing HAM-D-17 total scores, starting at week 2.
The estimated probability of remission for duloxetine-treated patients
(44%) was almost 3 times that of placebo patients (16%). Duloxetine
significantly reduced **painful** physical symptoms in comparison
with placebo. Discontinuation due to adverse events for
duloxetine-treated patients (13.8%) compared favorably with the rates
reported for SSRIs in other studies. Nausea, dry mouth, and somnolence
were the most common adverse events; no significant incidence of
hypertension was seen. CONCLUSION: Duloxetine, 60 mg/day, is a
well-tolerated and effective treatment for MDD that reduces
painful physical symptoms. These findings suggest that duloxetine
may be a first-line treatment for patients with MDD and associated

painful physical symptoms.

CT Check Tags: Comparative Study; Female; Male
Adult

Antidepressive Agents: AD, administration & dosage

***Antidepressive Agents: TU, therapeutic use**

Depressive Disorder: DI, diagnosis

***Depressive Disorder: DT, drug therapy**

Depressive Disorder: PX, psychology

Dose-Response Relationship, Drug

Double-Blind Method

Drug Administration Schedule

Humans

Pain Measurement

Placebos

Psychiatric Status Rating Scales

Somatoform Disorders: DI, diagnosis

***Somatoform Disorders: DT, drug therapy**

Somatoform Disorders: PX, psychology

Thiophenes: AD, administration & dosage

***Thiophenes: TU, therapeutic use**

Treatment Outcome

RN 116539-58-3 (duloxetine)

CN 0 (**Antidepressive Agents**); 0 (Placebos); 0 (Thiophenes)

L91 ANSWER 19 OF 313 MEDLINE on STN DUPLICATE 28

ACCESSION NUMBER: 2002259683 MEDLINE

DOCUMENT NUMBER: PubMed ID: 12000200

TITLE: Does **depression** hurt?.

AUTHOR: Stahl Stephen M

CORPORATE SOURCE: Neuroscience Education Institute in Carlsbad, CA 92009,
USA.

SOURCE: Journal of clinical psychiatry, (2002 Apr) 63 (4) 273-4.
Journal code: 7801243. ISSN: 0160-6689.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200205

ENTRY DATE: Entered STN: 20020510

Last Updated on STN: 20020602

Entered Medline: 20020531

AB **Depression** is an illness that causes symptoms in both the body and the brain, i.e., **painful** physical as well as emotional and vegetative symptoms. Ascending serotonergic and noradrenergic pathways may mediate the emotional and vegetative symptoms of **depression** and can potentially be targets of **serotonin** and **norepinephrine reuptake inhibitors** to obtain relief of these symptoms. Descending serotonergic and noradrenergic pathways may regulate the **painful** physical symptoms of **depression**, and when targeted by **serotonin** and **norepinephrine reuptake inhibitors**, relieve these symptoms as well. Selective serotonin **reuptake inhibitors** have a remission rate of 35%, and dual-action **reuptake inhibitors** have a 45% remission rate. Despite these results, the best treatment of **depression** currently recognizes the 3 types of symptoms and targets them all for complete remission no matter which drug is used.

CT ***Affective Symptoms: DI, diagnosis**
Affective Symptoms: DT, drug therapy

Affective Symptoms: PP, physiopathology
 Antidepressive Agents: PD, pharmacology
 Antidepressive Agents: TU, therapeutic use
 *Depressive Disorder: DI, diagnosis
 Depressive Disorder: DT, drug therapy
 Depressive Disorder: PP, physiopathology

Humans

Norepinephrine: PH, physiology

*Pain: DI, diagnosis

Pain: DT, drug therapy

Pain: PP, physiopathology

Serotonin: PH, physiology

Serotonin Uptake Inhibitors: PD, pharmacology

Serotonin Uptake Inhibitors: TU, therapeutic use

RN 50-67-9 (Serotonin); 51-41-2 (Norepinephrine)

CN 0 (Antidepressive Agents); 0 (Serotonin Uptake Inhibitors)

L91 ANSWER 20 OF 313 MEDLINE on STN DUPLICATE 29
 ACCESSION NUMBER: 2001250130 MEDLINE
 DOCUMENT NUMBER: PubMed ID: 11346061
 TITLE: Treatment of neuropathic pain with venlafaxine.
 AUTHOR: Sumpton J E; Moulin D E
 CORPORATE SOURCE: Pharmacy Department, London Health Sciences Centre, Ontario, Canada.. janice.sumpton@lhsc.on.ca
 SOURCE: Annals of pharmacotherapy, (2001 May) 35 (5) 557-9. Journal code: 9203131. ISSN: 1060-0280.
 PUB. COUNTRY: United States
 DOCUMENT TYPE: (CASE REPORTS)
 Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 200109
 ENTRY DATE: Entered STN: 20010924
 Last Updated on STN: 20010924
 Entered Medline: 20010920

AB OBJECTIVE: To report a case of successful treatment of neuropathic pain with venlafaxine. CASE REPORT: A 39-year-old white woman presented with neuropathic back pain. The patient obtained 50% pain relief with consecutive use of amitriptyline, desipramine, and imipramine. Anticholinergic effects prompted a switch to extended-release venlafaxine 75 mg/d. Pain relief was as effective with this therapy as with the tricyclic antidepressants. The absence of adverse effects allowed the patient to discontinue all laxatives. DISCUSSION: Venlafaxine is an antidepressant that inhibits reuptake of norepinephrine and serotonin. This is the major mechanism by which tricyclic antidepressants relieve neuropathic pain. Venlafaxine does not bind to muscarinic-cholinergic, histaminic or alpha1-adrenergic receptors responsible for the common adverse effects seen with tricyclic antidepressants. CONCLUSIONS: This report describes the efficacious use of venlafaxine in the treatment of neuropathic pain. Double-blind, randomized, controlled trials are needed to explore this further.

CT Check Tags: Female

Adult

*Cyclohexanols: TU, therapeutic use

Humans

*Pain: DT, drug therapy

*Peripheral Nervous System Diseases: DT, drug therapy

*Serotonin Uptake Inhibitors: TU, therapeutic use

Treatment Outcome

RN 93413-69-5 (venlafaxine)

CN 0 (Cyclohexanols); 0 (Serotonin Uptake Inhibitors)

L91 ANSWER 21 OF 313 MEDLINE on STN

ACCESSION NUMBER: 2005530048 IN-PROCESS

DOCUMENT NUMBER: PubMed ID: 16206355

TITLE: Efficacy of milnacipran in patients with fibromyalgia.

AUTHOR: Gendreau R Michael; Thorn Michael D; Gendreau Judy F;
Kranzler Jay D; Ribeiro Saulo; Gracely Richard H; Williams
David A; Mease Philip J; McLean Samuel A; Clauw Daniel J

CORPORATE SOURCE: Cypress Biosciences, 4350 Executive Drive, San Diego, CA
92121, USA.. mgendreau1@cypressbio.com

SOURCE: Journal of rheumatology, (2005 Oct) 32 (10) 1975-85.
Journal code: 7501984. ISSN: 0315-162X.

PUB. COUNTRY: Canada

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: NONMEDLINE; IN-PROCESS; NONINDEXED; Priority Journals

ENTRY DATE: Entered STN: 20051006

Last Updated on STN: 20051028

AB OBJECTIVE: Fibromyalgia (FM) is a common musculoskeletal condition characterized by widespread **pain**, tenderness, and a variety of other somatic symptoms. Current treatments are modestly effective. Arguably, the best studied and most effective compounds are tricyclic **antidepressants** (TCA). Milnacipran, a nontricyclic compound that **inhibits** the **reuptake** of both **serotonin** and **norepinephrine**, may provide many of the beneficial effects of TCA with a superior side effect profile. METHODS: One hundred twenty-five patients with FM were randomly assigned in a 3:3:2 ratio to receive milnacipran twice daily, milnacipran once daily, or placebo for 3 months in a double-blind dose-escalation trial; 92% of twice-daily and 81% of once-daily participants achieved dose escalation to the target milnacipran dose of 200 mg. RESULTS: The primary endpoint was reduction of **pain**. Both the once- and twice-daily groups showed statistically significant improvements in **pain**, as well as improvements in global well being, fatigue, and other domains. Response rates for patients receiving milnacipran were equal in patients with and without comorbid **depression**, but placebo response rates were considerably higher in **depressed** patients, leading to significantly greater overall efficacy in the **nondepressed** group. CONCLUSION: In this Phase II study, milnacipran led to statistically significant improvements in **pain** and other symptoms of FM. The effect sizes were equal to those previously found with TCA, and the drug was generally well tolerated.

L91 ANSWER 22 OF 313 MEDLINE on STN

ACCESSION NUMBER: 2005261994 MEDLINE

DOCUMENT NUMBER: PubMed ID: 15902759

TITLE: Current trends in neuropathic **pain** treatments
with special reference to fibromyalgia.

AUTHOR: Offenbaecher Martin; Ackenheil Manfred

CORPORATE SOURCE: Department of Medical Psychology, University of Munich
Medical School, Goethestrasse 31, 80336 Munchen, Germany..
Martin.Offenbaecher@med.uni-muenchen.de

SOURCE: CNS spectrums, (2005 Apr) 10 (4) 285-97. Ref: 74
Journal code: 9702877. ISSN: 1092-8529.

PUB. COUNTRY: United States
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
 General Review; (REVIEW)
 (REVIEW OF REPORTED CASES)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 200506
 ENTRY DATE: Entered STN: 20050521
 Last Updated on STN: 20050624
 Entered Medline: 20050623

AB Neuropathic **pain** and fibromyalgia are prevalent diseases which have major consequences on healthcare resources and the individual. From the clinical point of view neuropathic **pains** represent a heterogeneous group of aetiologically different diseases ranging from cancer to diabetes. Patients with fibromyalgia also display clinical features common in neuropathic **pain** suggesting that there might be some overlap. The mechanisms responsible for symptoms and signs in both diseases are still unknown. Recently, there have been numerous reports of various pharmacological treatments of neuropathic **pain** and fibromyalgia with often disappointing results. Most of the studies were of short duration, had high attrition rates, and displayed other methodological problems. Some compounds had high rates of adverse effects which makes it often difficult for the patients to tolerate the treatment, especially in the long-term. At present, the best options for medication treatment are tricyclic **antidepressants** in lower dosage than usual in psychiatric disorders and a wide range of anticonvulsants. Opioids are sometimes recommended but have been found to have minor efficacy. Recently, there have been more controlled trials, which are reported here if they had been published between 2002 and 2004. Various compounds have been tested in different studies. Treatment of fibromyalgia, which has many features in common with **depressive** symptoms, became the focus of interest. New promising studies with dual **serotonin-norepinephrine reuptake inhibitors** (duloxetine and milnacipram) and a newer antiepileptic drug (pregabalin) are in progress. Future research will have to apply new approaches (e.g., using a mechanism-based classification of neuropathic **pain** and carrying out studies in populations with the same symptom but not necessarily the same disease) in order to find effective treatments for these common and often debilitating diseases.

CT *Analgesics: TU, therapeutic use
 *Analgesics, Opioid: TU, therapeutic use
 *Anticonvulsants: TU, therapeutic use
 *Fibromyalgia: DT, drug therapy
 Humans
 *Ketamine: TU, therapeutic use
 *N-Methylaspartate: AI, antagonists & inhibitors
 *N-Methylaspartate: TU, therapeutic use
 Needs Assessment
 *Neuralgia: DT, drug therapy

RN 6384-92-5 (N-Methylaspartate); 6740-88-1 (Ketamine)

CN 0 (Analgesics); 0 (Analgesics, Opioid); 0 (Anticonvulsants)

L91 ANSWER 23 OF 313 MEDLINE on STN

ACCESSION NUMBER: 2005296409 MEDLINE

DOCUMENT NUMBER: PubMed ID: 15870506

TITLE: Effects of venlafaxine treatment on clozapine plasma levels in schizophrenic patients.

AUTHOR: Repo-Tiihonen Eila; Eloranta Anne; Hallikainen Tero; Tiihonen Jari

CORPORATE SOURCE: Department of Forensic Psychiatry, University of Kuopio, Niuvanniemi Hospital, FI-70240 Kuopio, Finland.

SOURCE: Neuropsychobiology, (2005) 51 (4) 173-6. Electronic Publication: 2005-05-04. Journal code: 7512895. ISSN: 0302-282X.

PUB. COUNTRY: Switzerland

DOCUMENT TYPE: (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200507

ENTRY DATE: Entered STN: 20050609
Last Updated on STN: 20050731
Entered Medline: 20050729

AB Depressive symptoms are found at any stage of schizophrenia, and antidepressant medication may be beneficial. Selective serotonin reuptake inhibitor antidepressants have been considered safe in schizophrenia but in combination with clozapine, that is widely used in chronic treatment-resistant schizophrenia, remarkable pharmacokinetic interactions can occur causing an elevation in clozapine plasma levels. To investigate this further, the plasma levels of clozapine were measured in 11 schizophrenic male patients with depressive symptoms who were administered both clozapine and venlafaxine. Low to moderate doses of venlafaxine did not seem to have any significant effect on clozapine plasma levels. Copyright (c) 2005 S. Karger AG, Basel.

CT Check Tags: Comparative Study; Male
Adult
*Antidepressive Agents, Second-Generation: TU, therapeutic use
*Antipsychotic Agents: BL, blood
Antipsychotic Agents: TU, therapeutic use
Chromatography, High Pressure Liquid: MT, methods
*Clozapine: BL, blood
Clozapine: TU, therapeutic use
*Cyclohexanols: PD, pharmacology
Cyclohexanols: TU, therapeutic use
Depression: BL, blood
Depression: DT, drug therapy
Depression: ET, etiology
Humans
Middle Aged
*Schizophrenia: BL, blood
Schizophrenia: CO, complications
Schizophrenia: DT, drug therapy

RN 5786-21-0 (Clozapine); 93413-69-5 (venlafaxine)

CN 0 (Antidepressive Agents, Second-Generation); 0 (Antipsychotic Agents); 0 (Cyclohexanols)

L91 ANSWER 24 OF 313 MEDLINE on STN

ACCESSION NUMBER: 2005069884 MEDLINE

DOCUMENT NUMBER: PubMed ID: 15698358

TITLE: Bilateral acute angle closure caused by supraciliary effusions associated with venlafaxine intake.

COMMENT: Erratum in: Med J Aust. 2005 Mar 21;182(6):312

AUTHOR: de Guzman Maria Hannah Pia; Thiagalingam Sureka; Ong Poh Yan; Goldberg Ivan

CORPORATE SOURCE: Glaucoma Unit, Sydney Eye Hospital, Sydney, NSW.

SOURCE: Medical journal of Australia, (2005 Feb 7) 182 (3) 121-3. Journal code: 0400714. ISSN: 0025-729X.

PUB. COUNTRY: Australia

DOCUMENT TYPE: (CASE REPORTS)
 Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 200504
 ENTRY DATE: Entered STN: 20050209
 Last Updated on STN: 20050427
 Entered Medline: 20050426

CT Check Tags: Male
 Adult

*Antidepressive Agents, Second-Generation: AE, adverse effects
 Antihypertensive Agents: TU, therapeutic use
 Anxiety: CO, complications
 Anxiety: DT, drug therapy
 *Ciliary Body: US, ultrasonography
 *Cyclohexanols: AE, adverse effects
 Depression: CO, complications
 Depression: DT, drug therapy
 *Glaucoma, Angle-Closure: CI, chemically induced
 Glaucoma, Angle-Closure: TH, therapy
 Glaucoma, Angle-Closure: US, ultrasonography
 Gonioscopy
 Humans
 Iris: SU, surgery
 Microscopy, Acoustic
 Ocular Hypertension: CI, chemically induced
 Ocular Hypertension: DT, drug therapy
 Ocular Hypertension: US, ultrasonography

RN 93413-69-5 (venlafaxine)

CN 0 (Antidepressive Agents, Second-Generation); 0 (Antihypertensive Agents);
 0 (Cyclohexanols)

L91 ANSWER 25 OF 313 MEDLINE on STN

ACCESSION NUMBER: 2005319495 MEDLINE

DOCUMENT NUMBER: PubMed ID: 15927394

TITLE: Duloxetine vs. placebo in patients with **painful**
 diabetic neuropathy.

AUTHOR: Goldstein David J; Lu Yili; Detke Michael J; Lee Thomas C;
 Iyengar Smriti

CORPORATE SOURCE: PRN Consulting and Department of Pharmacology and
 Toxicology, Indiana University School of Medicine,
 Indianapolis, IN 46285, USA.

SOURCE: Pain, (2005 Jul) 116 (1-2) 109-18.
 Journal code: 7508686. ISSN: 0304-3959.

PUB. COUNTRY: Netherlands

DOCUMENT TYPE: (CLINICAL TRIAL)
 Journal; Article; (JOURNAL ARTICLE)
 (RANDOMIZED CONTROLLED TRIAL)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200508

ENTRY DATE: Entered STN: 20050622
 Last Updated on STN: 20050831
 Entered Medline: 20050830

AB The aim of this study was to examine the efficacy and safety of
 duloxetine, a balanced and potent dual **reuptake**
inhibitor of **serotonin** and **norepinephrine**, in
 the management of diabetic peripheral neuropathic **pain**.
Serotonin and **norepinephrine** are thought to inhibit

pain via descending **pain** pathways. In a 12-week, multicenter, double-blind study, 457 patients experiencing **pain** due to polyneuropathy caused by Type 1 or Type 2 diabetes mellitus were randomly assigned to treatment with duloxetine 20 mg/d (20 mg QD), 60 mg/d (60 mg QD), 120 mg/d (60 mg BID), or placebo. The diagnosis was confirmed by a score of at least 3 on the Michigan Neuropathy Screening Instrument. The primary efficacy measure was the weekly mean score of the 24-h Average **Pain** Score, which was rated on an 11-point (0-10) Likert scale (no **pain** to worst possible **pain**) and computed from diary scores between two site visits. Duloxetine 60 and 120 mg/d demonstrated statistically significant greater improvement compared with placebo on the 24-h Average **Pain** Score, beginning 1 week after randomization and continuing through the 12-week trial. Duloxetine also separated from placebo on nearly all the secondary measures including health-related outcome measures. Significantly more patients in all three active-treatment groups achieved a 50% reduction in the 24-h Average **Pain** Score compared with placebo. Duloxetine treatment was considered to be safe and well tolerated with less than 20 percent discontinuation due to adverse events. Duloxetine at 60 and 120 mg/d was safe and effective in the management of diabetic peripheral neuropathic **pain**.

CT Check Tags: Comparative Study; Female; Male
 Aged
 Demography
 Depression: DT, drug therapy
 Depression: ET, etiology
 Diabetic Neuropathies: BL, blood
 Diabetic Neuropathies: CO, complications
 *Diabetic Neuropathies: DT, drug therapy
 Diabetic Neuropathies: UR, urine
 Dose-Response Relationship, Drug
 Double-Blind Method
 Humans
 Middle Aged
 Pain Measurement: DE, drug effects
 Pain Measurement: MT, methods
 Personality Inventory
 *Placebos: TU, therapeutic use
 Serotonin Uptake Inhibitors: BL, blood
 *Serotonin Uptake Inhibitors: TU, therapeutic use
 Serotonin Uptake Inhibitors: UR, urine
 Thiophenes: BL, blood
 *Thiophenes: TU, therapeutic use
 Thiophenes: UR, urine
 Treatment Outcome
 RN 116539-58-3 (duloxetine)
 CN 0 (Placebos); 0 (Serotonin Uptake Inhibitors); 0 (Thiophenes)

L91 ANSWER 26 OF 313 MEDLINE on STN
 ACCESSION NUMBER: 2005479567 MEDLINE
 DOCUMENT NUMBER: PubMed ID: 16103866
 TITLE: Duloxetine (Cymbalta) for diabetic neuropathic **pain**
 .
 AUTHOR: Anonymous
 SOURCE: Medical letter on drugs and therapeutics, (2005 Aug 15-29)
 47 (1215-1216) 67-8.
 Journal code: 2985240R. ISSN: 0025-732X.
 PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200509
ENTRY DATE: Entered STN: 20050911
Last Updated on STN: 20050914
Entered Medline: 20050913

AB A selective **serotonin and norepinephrine reuptake inhibitor** approved for **depression** and now also for diabetic peripheral neuropathy.

CT Check Tags: Female; Male
Antidepressive Agents: AE, adverse effects
*Antidepressive Agents: TU, therapeutic use
Clinical Trials
*Diabetic Neuropathies: DT, drug therapy
Humans
Nausea: CI, chemically induced
*Pain: DT, drug therapy
Pain Measurement: MT, methods
Thiophenes: AE, adverse effects
*Thiophenes: TU, therapeutic use

RN 116539-58-3 (duloxetine)

CN 0 (Antidepressive Agents); 0 (Thiophenes)

L91 ANSWER 27 OF 313 MEDLINE on STN

ACCESSION NUMBER: 2005073985 MEDLINE

DOCUMENT NUMBER: PubMed ID: 15704030

TITLE: [Effectiveness of venlafaxine in the treatment of alcohol dependence with comorbid depression].
Efectividad de la venlafaxina en el tratamiento de la dependencia de alcohol con depresion comorbida.

AUTHOR: Garcia-Portilla M P; Bascaran M T; Saiz P A; Mateos M; Gonzalez-Quiros M; Perez P; Avila J J; Torres M A; Bombin B; Caso C; Marin R; Prieto R; Bobes J

CORPORATE SOURCE: Area de Psiquiatria, Universidad de Oviedo, Oviedo..
albert@uniovi.es

SOURCE: Actas espanolas de psiquiatria, (2005 Jan-Feb) 33 (1) 41-5.
Journal code: 100886502. ISSN: 1139-9287.

PUB. COUNTRY: Spain

DOCUMENT TYPE: (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(MULTICENTER STUDY)

LANGUAGE: Spanish

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200505

ENTRY DATE: Entered STN: 20050211
Last Updated on STN: 20050601
Entered Medline: 20050531

AB INTRODUCTION: There are no conclusive data on the effectiveness of antidepressant drugs in the treatment of comorbid cases of alcohol dependence and depression. OBJECTIVES: To determine the effectiveness of venlafaxine on depression and on severity (need of treatment) of alcohol dependence and related problems. METHODS: Observational, open-label, multicenter, 24-week follow-up study. PATIENTS: 90 outpatients with diagnosis of alcohol dependence and associated major depression disorder (DSMIV criteria). Outcomes measures: the Hamilton Rating Scale for Depression (HAM-D17), European Addiction Severity Index (EuropASI) and Clinical Global Impression, severity and improvement subscales, (CGI-S and CGI-I). Evaluations were performed at baseline and at weeks 2, 4, 8 and

24. RESULTS: Mean age 44.94+/-9.74 years; 73.3 % man. HAM-D17 mean scores significantly decreased from baseline (24.85+/-5.94) to week 24 (5.976+/-4.68) and at each of the follow-up visits vs previous visit (p < 0.0005). Significant decreases from baseline to week 24 were obtained in four areas of EuropASI: medical status (2.12+/-2.45 to 1.07+/-1.68), alcohol use (5.29+/-2.24 to 3.04+/-2.35), family/ social relationships (3.68+/-2.36 to 1.71+/-2.06) and psychiatric status (5.61+/-1.81 to 2.67+/-2.03). Tolerance was excellent or good in 76.7% of the patients. CONCLUSIONS: Venlafaxine demonstrated to be effective in the treatment of depressive alcoholic patients. Furthermore, it seems to be useful to decrease the severity of problems related with the alcohol use.

CT Check Tags: Female; Male

Adult

*Alcoholism: CO, complications

*Alcoholism: DT, drug therapy

*Antidepressive Agents, Second-Generation: TU, therapeutic use

*Cyclohexanols: TU, therapeutic use

*Depression: CO, complications

*Depression: DT, drug therapy

English Abstract

Follow-Up Studies

Humans

RN 93413-69-5 (venlafaxine)

CN 0 (Antidepressive Agents, Second-Generation); 0 (Cyclohexanols)

L91 ANSWER 28 OF 313 MEDLINE on STN

ACCESSION NUMBER: 2005232599 MEDLINE

DOCUMENT NUMBER: PubMed ID: 15866490

TITLE: Simultaneous determination of fluoxetine, citalopram, paroxetine, venlafaxine in plasma by high performance liquid chromatography-electrospray ionization mass spectrometry (HPLC-MS/ESI).

AUTHOR: Juan He; Zhiling Zhou; Huande Li

CORPORATE SOURCE: Clinical Pharmaceutical Research Institute, Second Xiangya Hospital, Central South University, Changsha 410011, PR China.. hejuanwin@126.com

SOURCE: Journal of chromatography. B, Analytical technologies in the biomedical and life sciences, (2005 Jun 5) 820 (1) 33-9. Electronic Publication: 2005-04-11. Journal code: 101139554. ISSN: 1570-0232.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (VALIDATION STUDIES)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200508

ENTRY DATE: Entered STN: 20050504

Last Updated on STN: 20050820

Entered Medline: 20050819

AB Fluoxetine, citalopram, paroxetine and venlafaxine have been widely used in the treatment of depression. However, no study has been conducted to determine the four drugs simultaneously by high performance liquid chromatography-electrospray ionization mass spectrometry (HPLC-MS/ESI). OBJECTIVE: To establish a new, rapid and sensitive HPLC-MS/ESI method for simultaneous determination and screening in human plasma of the four most commonly prescribed nontricyclic antidepressants: fluoxetine, citalopram, paroxetine and venlafaxine. METHODS: The analytes in plasma were extracted by solid-phase-extraction column after samples had been alkalinized. The HPLC separation of the analytes was performed on a

MACHEREY-NAGEL C(18) (250 mmx4.6 mm, 5 microm, Germany) column, using water (formic acid 0.6 per thousand, ammonium acetate: 30 mmol/l)-acetonitrile (35:65, v/v) as mobile phase, with a flow-rate of 0.85 ml/min. The compounds were ionized in the electrospray ionization (ESI) ion source of the mass spectrometer and were detected in the selected ion recording (SIR) mode. RESULTS: The calibration curves were linear in the 5.0-1000.0 ng/ml range for all compounds, all of them with coefficients of determination above 0.9900. The average extraction recoveries for all the four analytes were above 73.2%. The methodology recoveries were higher than 95.0%. The limits of detection (LODs) were 0.5, 0.3, 0.3 and 0.1 ng/ml for fluoxetine, citalopram, paroxetine and venlafaxine, respectively. The intra- and inter-day variation coefficients were less than 15.0%. CONCLUSION: The method is accurate, sensitive and simple for routine therapeutic drug monitoring (TDM) as well as toxicologic screening, and for the study of the pharmacokinetics and metabolism of the four drugs.

CT Check Tags: Female; Male

*Antidepressive Agents, Tricyclic: BL, blood

*Chromatography, High Pressure Liquid: MT, methods

*Citalopram: BL, blood

*Cyclohexanols: BL, blood

Depression: DT, drug therapy

*Fluoxetine: BL, blood

Humans

*Paroxetine: BL, blood

Reproducibility of Results

Sensitivity and Specificity

*Spectrometry, Mass, Electrospray Ionization: MT, methods

RN 54910-89-3 (Fluoxetine); 59729-33-8 (Citalopram); 61869-08-7 (Paroxetine); 93413-69-5 (venlafaxine)

CN 0 (Antidepressive Agents, Tricyclic); 0 (Cyclohexanols)

L91 ANSWER 29 OF 313 MEDLINE on STN

ACCESSION NUMBER: 2005008390 MEDLINE

DOCUMENT NUMBER: PubMed ID: 15633860

TITLE: Spontaneous orgasm started with venlafaxine and continued with citalopram.

AUTHOR: Yanik Medaim

SOURCE: Canadian journal of psychiatry. Revue canadienne de psychiatrie, (2004 Nov) 49 (11) 786.

Journal code: 7904187. ISSN: 0706-7437.

PUB. COUNTRY: Canada

DOCUMENT TYPE: (CASE REPORTS)

Letter

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200502

ENTRY DATE: Entered STN: 20050107

Last Updated on STN: 20050209

Entered Medline: 20050208

CT Check Tags: Female

Ambulatory Care

*Antidepressive Agents, Second-Generation: PD, pharmacology

*Antidepressive Agents, Second-Generation: TU, therapeutic use

*Citalopram: PD, pharmacology

*Citalopram: TU, therapeutic use

Combined Modality Therapy

*Cyclohexanols: PD, pharmacology

*Cyclohexanols: TU, therapeutic use

*Depression: DT, drug therapy
 *Depression: RH, rehabilitation
 Depression: TH, therapy
 Electroconvulsive Therapy: MT, methods
 Humans
 Middle Aged

*Orgasm: DE, drug effects
 Patient Admission

RN 59729-33-8 (Citalopram); 93413-69-5 (venlafaxine)
 CN 0 (Antidepressive Agents, Second-Generation); 0 (Cyclohexanols)

L91 ANSWER 30 OF 313 MEDLINE on STN
 ACCESSION NUMBER: 2004398531 MEDLINE
 DOCUMENT NUMBER: PubMed ID: 15303249
 TITLE: Very low dose quetiapine-induced galactorrhea in
 combination with venlafaxine.
 AUTHOR: Pae Chi-Un; Kim Jung-Jin; Lee Chang-Uk; Chae Jeong-Ho; Lee
 Soo-Jung; Lee Chul; Paik In-Ho
 SOURCE: Human psychopharmacology, (2004 Aug) 19 (6) 433-4.
 Journal code: 8702539. ISSN: 0885-6222.
 PUB. COUNTRY: England: United Kingdom
 DOCUMENT TYPE: (CASE REPORTS)
 Letter
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 200501
 ENTRY DATE: Entered STN: 20040811
 Last Updated on STN: 20050111
 Entered Medline: 20050110

CT Check Tags: Female
 Adult

*Antidepressive Agents, Second-Generation: AE, adverse effects
 Antidepressive Agents, Second-Generation: TU, therapeutic use
 Antipsychotic Agents: AE, adverse effects
 Antipsychotic Agents: TU, therapeutic use
 *Cyclohexanols: AE, adverse effects
 Cyclohexanols: TU, therapeutic use
 Depression: DT, drug therapy
 Depression: ME, metabolism
 *Dibenzothiazepines: AE, adverse effects
 Dibenzothiazepines: TU, therapeutic use
 Drug Synergism
 Drug Therapy, Combination
 *Galactorrhea: CI, chemically induced
 Humans
 Prolactin: ME, metabolism

RN 9002-62-4 (Prolactin); 93413-69-5 (venlafaxine)
 CN 0 (Antidepressive Agents, Second-Generation); 0 (Antipsychotic Agents); 0
 (Cyclohexanols); 0 (Dibenzothiazepines); 0 (quetiapine)

L91 ANSWER 31 OF 313 MEDLINE on STN
 ACCESSION NUMBER: 2004496359 MEDLINE
 DOCUMENT NUMBER: PubMed ID: 15449363
 TITLE: An open trial of venlafaxine for the treatment of late-life
 atypical depression.
 AUTHOR: Roose Steven P; Miyazaki Marissa; Devanand Dev; Seidman
 Stuart; Fitzsimmons Linda; Turret Nancy; Sackeim Harold
 CORPORATE SOURCE: New York State Psychiatric Institute, College of Physicians
 and Surgeons of Columbia University, New York 10032, USA..

spr2@columbia.edu
CONTRACT NUMBER: MH55716 (NIMH)
SOURCE: International journal of geriatric psychiatry, (2004 Oct)
19 (10) 989-94.
Journal code: 8710629. ISSN: 0885-6230.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200503
ENTRY DATE: Entered STN: 20041007
Last Updated on STN: 20050311
Entered Medline: 20050310

AB OBJECTIVES: The atypical subtype in patients with major depressive disorder is characterized by mood reactivity, significant weight gain or increase in appetite, hypersomnia, leaden paralysis and a long-standing pattern of interpersonal rejection sensitivity. Though atypical depression is well documented in younger patients, little attention has been paid to the atypical subtype in samples of late-life depressed patients. This study reports the patient characteristics and treatment results of an eight-week open-label trial of venlafaxine in a sample of older depressed patients with atypical subtype. METHODS: Patients received fixed dosing schedule (up to 300 mg/day) of venlafaxine (Effexor XR) for 8 weeks. RESULTS: In this sample of 17 patients, the mean age was 65.6 years and 77% were female. Most strikingly, 53% of patients presented with late-onset atypical depression defined as first episode after the age of 50. Fifteen of the 17 patients (88%) completed the eight-week treatment trial. The mean score on the HRSD 24-item decreased from 22.2 +/- 5.1 at baseline to 11.8 +/- 8.9 ($p < 0.001$), and the mean total atypical item score decreased from 6.2 +/- 1.6 to 2.8 +/- 2.0 ($p < 0.001$). Remission was defined as a final HRSD ≤ 10 and a 50% reduction in baseline HRSD score. The intent-to-treat remission rate was 65% and the completer remission rate was 73%. CONCLUSIONS: In this sample of late-life patients with atypical depression venlafaxine treatment was reasonably effective and well tolerated. However, the effectiveness of venlafaxine in this study must be considered in the context that this was an open trial of antidepressant medication. Insufficient attention has been given to the atypical subtype in late-life depression. Whether late-onset atypical depression is significantly different from early-onset atypical depression, and whether late-onset patients with atypical depression are significantly different from late-onset patients with other depressive subtypes are questions of compelling interest.

CT Check Tags: Female; Male
Age of Onset
Aged
*Antidepressive Agents: TU, therapeutic use
Chi-Square Distribution
*Cyclohexanols: TU, therapeutic use
*Depression: DT, drug therapy
Depression: PX, psychology
Humans
Middle Aged
Research Support, Non-U.S. Gov't
Research Support, U.S. Gov't, P.H.S.

RN 93413-69-5 (venlafaxine)
CN 0 (Antidepressive Agents); 0 (Cyclohexanols)

L91 ANSWER 32 OF 313 MEDLINE on STN

ACCESSION NUMBER: 2004394278 MEDLINE
 DOCUMENT NUMBER: PubMed ID: 15298070
 TITLE: **Antidepressants** in the treatment of irritable
 bowel syndrome and visceral **pain** syndromes.
 AUTHOR: Crowell Michael D; Jones Michael P; Harris Lucinda A;
 Dineen Tisha N; Schettler V Ann; Olden Kevin W
 CORPORATE SOURCE: Division of Gastroenterology, Mayo Clinic College of
 Medicine and Mayo Foundation, Scottsdale, AZ 85259, USA..
 crowell.michael@mayo.edu
 SOURCE: Current opinion in investigational drugs (London, England :
 2000), (2004 Jul) 5 (7) 736-42. Ref: 58
 Journal code: 100965718. ISSN: 1472-4472.
 PUB. COUNTRY: England: United Kingdom
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
 General Review; (REVIEW)
 (REVIEW, TUTORIAL)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 200410
 ENTRY DATE: Entered STN: 20040810
 Last Updated on STN: 20041019
 Entered Medline: 20041018

AB Irritable bowel syndrome (IBS) is characterized by abdominal **pain**
 associated with disordered defecation, which may include urgency and
 altered stool frequency. Visceral **pain** syndromes, including
 IBS, may be effectively treated by a variety of therapies that modulate
 the interactions between the central and enteric nervous systems.
 Clinical observations and preliminary data suggest that
antidepressants may be efficacious for the treatment of these
 syndromes. The tricyclic **antidepressants** (TCAs) have been
 utilized most extensively in this area, but there is a need for more
 rigorous efficacy data. Serotonin, an important neurotransmitter in both
 the central and enteric nervous systems, modifies both motility and
 sensation in the gut. Recognition of the importance of serotonin in
 digestive motility and sensation has sparked interest in the use of agents
 that modify serotonergic transmission in visceral **pain**
 syndromes. Pharmacological therapeutics that modulate the biological
 amines (**serotonin**, **norepinephrine**, dopamine and
 catecholamines) both peripherally and within the central nervous system
 may offer more effective therapies for these disorders. The selective
 serotonin **reuptake inhibitors** are commonly used in
 clinical practice, but more rigorous, controlled studies are needed to
 determine their effects beyond the treatment of psychiatric comorbidity.
 The newer generation **antidepressants** may provide additional
 insight into the pathophysiology of the brain-gut interactions and their
 relationship to functional bowel disorders, providing new therapeutic
 interventions.

CT **Abdominal Pain: CO, complications**
 ***Abdominal Pain: DT, drug therapy**
 Abdominal Pain: PP, physiopathology
 Antidepressive Agents, Tricyclic: CL, classification
 ***Antidepressive Agents, Tricyclic: TU, therapeutic use**
 Chronic Disease
 Humans
 Irritable Bowel Syndrome: CO, complications
 *Irritable Bowel Syndrome: DT, drug therapy
 Irritable Bowel Syndrome: PP, physiopathology
 Molecular Structure
 Randomized Controlled Trials

Stress, Psychological: CO, complications
Stress, Psychological: PP, physiopathology
CN 0 (Antidepressive Agents, Tricyclic)

L91 ANSWER 33 OF 313 MEDLINE on STN
ACCESSION NUMBER: 2004487000 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15349012
TITLE: Efficacy and tolerability of premenstrual use of
venlafaxine (flexible dose) in the treatment of
premenstrual dysphoric disorder.
AUTHOR: Cohen Lee S; Soares Claudio N; Lyster Amy; Cassano Paolo;
Brandes Mina; Leblanc Giselle A
CORPORATE SOURCE: Perinatal and Reproductive Psychiatry Clinical Research
Program, Massachusetts General Hospital (MGH), Harvard
Medical School, Boston, MA 02114, USA..
LCOHEN2@PARTNERS.ORG
SOURCE: Journal of clinical psychopharmacology, (2004 Oct) 24 (5)
540-3.
Journal code: 8109496. ISSN: 0271-0749.
PUB. COUNTRY: United States
DOCUMENT TYPE: (CLINICAL TRIAL)
(CONTROLLED CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200501
ENTRY DATE: Entered STN: 20041001
Last Updated on STN: 20050129
Entered Medline: 20050128
AB The objective of this study was to examine the efficacy and tolerability
of intermittent dosing of venlafaxine for the treatment of premenstrual
dysphoric disorder. One hundred and twenty-four women aged 18 to 45
years, with regular menstrual cycles and who reported significant
premenstrual symptoms, were assessed prospectively to confirm their
diagnosis of premenstrual dysphoric disorder. Twenty subjects with
confirmed premenstrual dysphoric disorder entered a single-blind, placebo
phase (1 cycle). Placebo nonresponders (n = 12) received 2 cycles of
intermittent (premenstrual) treatment with venlafaxine (75 to 112.5 mg/d).
Subjects initiated treatment 14 days before the anticipated onset of
menses and discontinued it on the second day of bleeding. Doses could be
adjusted after cycle 1 based on subjects' response and tolerability.
Response to treatment was assessed based on changes in the Daily Rating
Severity of Problems and Premenstrual Tension Syndrome Questionnaire
scores from baseline (before the placebo cycle), as well as Clinical
Global Impression-Severity scores. Discontinuation symptoms were assessed
between treatment cycles, using the Discontinuation-Emergent Signs and
Symptoms questionnaire. Eleven subjects concluded 2 cycles of
intermittent dosing with venlafaxine. Nine subjects (81.8%) showed
satisfactory response based on Clinical Global Impression of < or = 2.
Changes in Daily Rating Severity of Problems scores and subscores
(depression, physical symptoms, and anger) and in Premenstrual Tension
Syndrome Questionnaire scores were significant (P < 0.05 for all
comparisons, Wilcoxon tests). Intermittent treatment was well tolerated.
This preliminary report suggests that premenstrual use of venlafaxine is
an efficacious and well-tolerated treatment for premenstrual dysphoric
disorder.
CT Check Tags: Female
Adult
*Antidepressive Agents, Second-Generation: AD, administration &

dosage**Antidepressive Agents, Second-Generation: AE, adverse effects*****Cyclohexanols: AD, administration & dosage**

Cyclohexanols: AE, adverse effects

Depression: DI, diagnosis***Depression: DT, drug therapy****Depression: PX, psychology**

Dose-Response Relationship, Drug

Drug Administration Schedule

Humans

Luteal Phase: DE, drug effects

Luteal Phase: PX, psychology

Premenstrual Syndrome: DI, diagnosis

***Premenstrual Syndrome: DT, drug therapy**

Premenstrual Syndrome: PX, psychology

Prospective Studies

Research Support, Non-U.S. Gov't

***Serotonin Uptake Inhibitors: AD, administration & dosage**

Serotonin Uptake Inhibitors: AE, adverse effects

Treatment Outcome

RN **93413-69-5 (venlafaxine)**CN 0 (Antidepressive Agents, Second-Generation); 0 (Cyclohexanols); 0
(Serotonin Uptake Inhibitors)

L91 ANSWER 34 OF 313 MEDLINE on STN

ACCESSION NUMBER: 2004282929 MEDLINE

DOCUMENT NUMBER: PubMed ID: 15182220

TITLE: New formulations of existing antidepressants: advantages in
the management of depression.

AUTHOR: Norman Trevor R; Olver James S

CORPORATE SOURCE: Department of Psychiatry, University of Melbourne, Austin &
Repatriation Medical Centre, Heidelberg, Victoria,
Australia.. trevorn@unimelb.edu.auSOURCE: CNS drugs, (2004) 18 (8) 505-20. Ref: 74
Journal code: 9431220. ISSN: 1172-7047.

PUB. COUNTRY: New Zealand

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200408

ENTRY DATE: Entered STN: 20040609

Last Updated on STN: 20040803

Entered Medline: 20040802

AB For nearly 50 years, antidepressant drugs have been the first-line treatment for various forms of depression. Despite their widespread use, these medications have significant shortcomings, in particular problems of patient compliance due to adverse effects. The introduction of new formulations of existing antidepressant medications may provide patients with benefits in terms of convenience of use. As a consequence, improvements in compliance may lead to better antidepressant efficiency. An orally disintegrating formulation of mirtazapine (mirtazapine SolTab), a once-weekly formulation of fluoxetine, an enantiomer-specific formulation of citalopram (escitalopram), an extended-release formulation of venlafaxine (venlafaxine XR), a controlled-release formulation of paroxetine (paroxetine CR) and intravenous formulations of some of the newer antidepressants have all been evaluated in limited clinical trials. In this article, a review of the pharmacokinetics and clinical evaluations

of these formulations is presented. While there do not appear to be major clinical advantages for the new formulations in terms of antidepressant efficacy, none of them is less efficacious than their older counterpart. Indeed, some of the new formulations are more acceptable to patients (fluoxetine once-weekly, paroxetine CR), others have pharmacokinetic advantages (venlafaxine XR, paroxetine CR), while others may have a faster onset of effect (mirtazapine SolTab, intravenous formulations). Further evaluation of some formulations is still required (mirtazapine SolTab, fluoxetine once-weekly), while others (venlafaxine XR, escitalopram) are finding widespread acceptance in clinical practice.

CT Animals

*Antidepressive Agents: CH, chemistry
 *Antidepressive Agents: TU, therapeutic use
 Antidepressive Agents, Second-Generation: CH, chemistry
 Antidepressive Agents, Second-Generation: PD, pharmacology
 Antidepressive Agents, Second-Generation: TU, therapeutic use
 Antidepressive Agents, Tricyclic: PD, pharmacology
 Antidepressive Agents, Tricyclic: TU, therapeutic use

Chemistry, Pharmaceutical

Cyclohexanols: CH, chemistry

Cyclohexanols: PD, pharmacology

Cyclohexanols: TU, therapeutic use

Delayed-Action Preparations

*Depression: DT, drug therapy

Drug Evaluation

Fluoxetine: CH, chemistry

Fluoxetine: PD, pharmacology

Fluoxetine: TU, therapeutic use

Humans

*Mianserin: AA, analogs & derivatives

Mianserin: CH, chemistry

Mianserin: PD, pharmacology

Mianserin: TU, therapeutic use

Molecular Conformation

Research Support, Non-U.S. Gov't

RN 24219-97-4 (Mianserin); 54910-89-3 (Fluoxetine); 61337-67-5 (mirtazapine);
 93413-69-5 (venlafaxine)

CN 0 (Antidepressive Agents); 0 (Antidepressive Agents, Second-Generation); 0
 (Antidepressive Agents, Tricyclic); 0 (Cyclohexanols); 0 (Delayed-Action
 Preparations)

L91 ANSWER 35 OF 313 MEDLINE on STN

ACCESSION NUMBER: 2004095608 MEDLINE

DOCUMENT NUMBER: PubMed ID: 14984621

TITLE: Mirtazapine is associated with less anxiolytic use among
 elderly depressed patients in long-term care facilities.

AUTHOR: Gardner Marie E; Malone Daniel C; Sey Mark; Babington Maude
 A

CORPORATE SOURCE: College of Pharmacy, The University of Arizona, Tucson, AZ,
 USA.. gardner@pharmacy.arizona.edu

SOURCE: Journal of the American Medical Directors Association,
 (2004 Mar-Apr) 5 (2) 101-6.

Journal code: 100893243. ISSN: 1525-8610.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200405

ENTRY DATE: Entered STN: 20040302

Last Updated on STN: 20040512

Entered Medline: 20040511

AB BACKGROUND: Depression is a common, treatable disorder among nursing facility residents. OBJECTIVE: The purpose of this study was to examine medication use and cost between two groups of patients: (1) persons treated with mirtazapine, as compared with (2) persons taking other antidepressants. DESIGN: This study was a retrospective chart review of long-term care patients. Consultant pharmacists collected data on patients who were receiving selective serotonin reuptake inhibitors (SSRIs), venlafaxine, nefazodone, or mirtazapine. SETTING: Nursing facilities that were geographically dispersed throughout the United States. PARTICIPANTS: We studied patients greater than 65 years of age with major depressive disorder or a depression-related diagnosis and receiving antidepressant treatment for at least 3 months. Patients with bipolar-induced depression were excluded as well as those receiving tricyclic antidepressants. RESULTS: The two groups were similar in terms of age, but those receiving mirtazapine had lower body weight and body mass index. Patients on mirtazapine were less likely to be taking a sedative/hypnotic ($P = 0.006$). This was primarily the result of fewer patients in the mirtazapine group taking lorazepam ($P = 0.03$). There was no difference between the two groups regarding their use of other psychotropic medications, including multiple antidepressants, antipsychotics, anticonvulsants, acetylcholinesterase inhibitors, or appetite stimulants. Monthly medication costs were less for those patients receiving mirtazapine (\$82.83) as compared with other antidepressants (\$97.03) ($P < 0.0001$). CONCLUSIONS: The results of this study suggest that patients receiving mirtazapine are less likely to be on anxiolytic/hypnotic agents. The findings also suggest that medication costs are less when mirtazapine is used compared with other antidepressants.

CT Check Tags: Comparative Study; Female; Male
Aged
Aged, 80 and over
Anti-Anxiety Agents: EC, economics
*Anti-Anxiety Agents: TU, therapeutic use
 Antidepressive Agents: EC, economics
 ***Antidepressive Agents: TU, therapeutic use**
Appetite Stimulants: TU, therapeutic use
Cyclohexanols: TU, therapeutic use
Dementia: CO, complications
 Depression: CO, complications
 ***Depression: DT, drug therapy**
Dietary Supplements: UT, utilization
Drug Costs: SN, statistics & numerical data
Drug Utilization Review
*Homes for the Aged: SN, statistics & numerical data
Humans
*Institutionalization: SN, statistics & numerical data
Long-Term Care
*Mianserin: AA, analogs & derivatives
Mianserin: EC, economics
*Mianserin: TU, therapeutic use
Research Support, Non-U.S. Gov't
Retrospective Studies
Serotonin Uptake Inhibitors: TU, therapeutic use
Triazoles: TU, therapeutic use
United States

RN 24219-97-4 (Mianserin); 61337-67-5 (mirtazapine); 83366-66-9 (nefazodone);
93413-69-5 (venlafaxine)

CN 0 (Anti-Anxiety Agents); 0 (Antidepressive Agents); 0 (Appetite Stimulants); 0 (Cyclohexanols); 0 (Serotonin Uptake Inhibitors); 0 (Triazoles)

L91 ANSWER 36 OF 313 MEDLINE on STN

ACCESSION NUMBER: 2005018942 MEDLINE

DOCUMENT NUMBER: PubMed ID: 15644856

TITLE: Pharmacologic management of neuropathic **pain**.

AUTHOR: Gordon Debra B; Love Georgette

CORPORATE SOURCE: University of Wisconsin Hospital and Clinics, 600 Highland Avenue, F6/121-1535, Madison, WI 53792, USA..
db.gordon@hosp.wisc.edu

SOURCE: Pain management nursing : official journal of the American Society of Pain Management Nurses, (2004 Dec) 5 (4 Suppl 1) 19-33. Ref: 89

Journal code: 100890606. ISSN: 1524-9042.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

General Review; (REVIEW)

(REVIEW, TUTORIAL)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200503

ENTRY DATE: Entered STN: 20050113

Last Updated on STN: 20050316

Entered Medline: 20050315

AB The mechanisms underlying the pathogenesis of neuropathic **pain** are complex but are gradually coming to light. Agents that have been found effective in a variety of neuropathic **pain** conditions include drugs that act to modulate (a) sodium or calcium channels, (b) N-methyl-D-aspartate receptors, (c) **norepinephrine** or **serotonin** reuptake, (d) opioid receptors, and (e) other cellular processes. Clinical trials have primarily evaluated these treatments for postherpetic neuralgia and **painful** diabetic neuropathy, the two most common types of neuropathic **pain**. Nonetheless, the identification of effective treatment regimens remains challenging, often because multiple mechanisms may be operating in a given patient giving rise to the same symptom. Alternatively, a single mechanism may be responsible for multiple symptoms. Currently available diagnostic tools are inadequate to determine the best treatment using a mechanism-based model. Clinically, drug treatment of neuropathic **pain** is often a matter of treatment trials. This article presents a summary of available clinical information on first-line and lesser-known treatments for neuropathic **pain**.

CT Analgesics: CL, classification

Analgesics: PD, pharmacology

*Analgesics: TU, therapeutic use

Anticonvulsants: TU, therapeutic use

Antidepressive Agents, Tricyclic: TU, therapeutic use

Calcium Channels: DE, drug effects

Clinical Trials

Drug Monitoring

Humans

*Nervous System Diseases: CO, complications

Neuromuscular Agents: TU, therapeutic use

Nurse's Role

Pain: DI, diagnosis

***Pain: DT, drug therapy**

***Pain: ET, etiology**

Pain: NU, nursing

Pain Measurement

Patient Selection

Receptors, N-Methyl-D-Aspartate: DE, drug effects

Receptors, Opioid: DE, drug effects

Serotonin Uptake Inhibitors: TU, therapeutic use

Sodium Channels: DE, drug effects

Treatment Outcome

CN 0 (Analgesics); 0 (Anticonvulsants); 0 (**Antidepressive Agents, Tricyclic**); 0 (Calcium Channels); 0 (Neuromuscular Agents); 0 (Receptors, N-Methyl-D-Aspartate); 0 (Receptors, Opioid); 0 (**Serotonin Uptake Inhibitors**); 0 (Sodium Channels)

L91 ANSWER 37 OF 313 MEDLINE on STN

ACCESSION NUMBER: 2004411632 MEDLINE

DOCUMENT NUMBER: PubMed ID: 15315473

TITLE: Common pathways of **depression** and **pain**.

AUTHOR: Delgado Pedro L

CORPORATE SOURCE: Department of Psychiatry, University Hospitals of Cleveland and Case Western Reserve University, Cleveland, Ohio 44106-5080, USA.. pedro.delgado@case.edu

SOURCE: Journal of clinical psychiatry, (2004) 65 Suppl 12 16-9. Ref: 30

Journal code: 7801243. ISSN: 0160-6689.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

General Review; (REVIEW)

(REVIEW, TUTORIAL)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200410

ENTRY DATE: Entered STN: 20040819

Last Updated on STN: 20041009

Entered Medline: 20041008

AB **Depressive** disorders are chronic conditions that produce both emotional and physical symptoms. Increasing evidence suggests that in some patients with **depressive** disorders a neurodegenerative process may occur, highlighting the importance of early and aggressive intervention. **Serotonin** (5-HT) and **norepinephrine** (NE) neurotransmitter systems influence neuroplasticity in the brain, and both are involved in mediating the therapeutic effects of most currently available **antidepressants**. Some dual-action **antidepressants** have been shown to be effective in managing the **pain** symptoms associated with **depression**. These agents may have advantages over others by treating a wider array of physical symptoms. Additionally, these agents may also have a role in modulating neurogenesis and other neuroplastic changes, thereby leading to more complete recovery in patients suffering from the emotional and physical symptoms of chronic **depression**.

CT **Adrenergic Uptake Inhibitors: TU, therapeutic use**

Antidepressive Agents: PD, pharmacology

Antidepressive Agents: TU, therapeutic use

Brain: DE, drug effects

*Brain: PP, physiopathology

Chronic Disease

Cyclohexanols: PD, pharmacology

Cyclohexanols: TU, therapeutic use

Depressive Disorder: DI, diagnosis

Depressive Disorder: DT, drug therapy

***Depressive Disorder: PP, physiopathology**
 Diabetic Neuropathies: DT, drug therapy
 Diabetic Neuropathies: PP, physiopathology
 Humans
 Neurodegenerative Diseases: DT, drug therapy
 Neurodegenerative Diseases: PP, physiopathology
 Neuronal Plasticity: DE, drug effects
 Neuronal Plasticity: PH, physiology
 Neurons: DE, drug effects
 Neurons: PH, physiology
***Norepinephrine: PH, physiology**
 Pain: DI, diagnosis
 Pain: DT, drug therapy
 ***Pain: PP, physiopathology**
 Recurrence
***Serotonin: PH, physiology**
 Serotonin Uptake Inhibitors: TU, therapeutic use
 Thiophenes: PD, pharmacology
 Thiophenes: TU, therapeutic use
 RN 116539-58-3 (duloxetine); 50-67-9 (Serotonin); 51-41-2 (Norepinephrine);
 93413-69-5 (venlafaxine)
 CN 0 (Adrenergic Uptake Inhibitors); 0 (
 Antidepressive Agents); 0 (Cyclohexanols); 0 (Serotonin
 Uptake Inhibitors); 0 (Thiophenes)

L91 ANSWER 38 OF 313 MEDLINE on STN
 ACCESSION NUMBER: 2005349170 MEDLINE
 DOCUMENT NUMBER: PubMed ID: 16001092
 TITLE: The link between **depression** and physical
 symptoms.
 AUTHOR: Trivedi Madhukar H
 CORPORATE SOURCE: University of Texas Southwest Medical School, Dallas
 75390-9119, USA.. madhukar.trivedi@utsouthwestern.edu
 SOURCE: Prim Care Companion J Clin Psychiatry, (2004) 6 (Suppl 1)
 12-6.
 Journal code: 100887410. ISSN: 1523-5998.
 PUB. COUNTRY: United States
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: NONMEDLINE; PUBMED-NOT-MEDLINE
 ENTRY MONTH: 200510
 ENTRY DATE: Entered STN: 20050708
 Last Updated on STN: 20051012
 Entered Medline: 20051011

AB Physical symptoms are common in **depression**, and, in fact, vague
 aches and **pain** are often the presenting symptoms of
depression. These symptoms include chronic joint **pain**,
 limb **pain**, back **pain**, gastrointestinal problems,
 tiredness, sleep disturbances, psychomotor activity changes, and appetite
 changes. A high percentage of patients with **depression** who seek
 treatment in a primary care setting report only physical symptoms, which
 can make **depression** very difficult to diagnose. Physical
pain and **depression** have a deeper biological connection
 than simple cause and effect; the neurotransmitters that influence both
pain and mood are **serotonin** and **norepinephrine**
 . Dysregulation of these transmitters is linked to both
depression and **pain**. **Antidepressants** that
inhibit the reuptake of both **serotonin** and
norepinephrine may be used as first-line treatments in

depressed patients who present with physical symptoms. Many physicians consider patients to be in remission when their acute emotional symptoms have abated, but residual symptoms--including physical symptoms--are very common and increase the likelihood of relapse. All symptoms must be measured in order to achieve full remission. There are a number of short yet accurate measurement tools (rating scales) available that effectively measure the remission of physical symptoms as well as emotional symptoms.

L91 ANSWER 39 OF 313 MEDLINE on STN
 ACCESSION NUMBER: 2004625937 MEDLINE
 DOCUMENT NUMBER: PubMed ID: 15600377
 TITLE: SNRIs in the management of acute major **depressive** disorder.
 AUTHOR: Zajecka John M; Albano Dominick
 CORPORATE SOURCE: Department of Psychiatry, Rush University Medical Center, Chicago, IL 60612, USA.. John_Zajecka@rush.edu
 SOURCE: Journal of clinical psychiatry, (2004) 65 Suppl 17 11-8. Ref: 68
 Journal code: 7801243. ISSN: 0160-6689.
 PUB. COUNTRY: United States
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
 General Review; (REVIEW)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 200502
 ENTRY DATE: Entered STN: 20041220
 Last Updated on STN: 20050202
 Entered Medline: 20050201

AB Remission of a patient's index major **depressive** episode is essential in preventing a recurrent or chronic **depressive** course. Once remission is established, the subsequent goal is to maintain remission and prevent a relapse of the episode with a minimum of 4 to 9 months of continuation treatment. Common belief suggests that all **antidepressants** have equivalent efficacy when measured by remission, but this may be a misconception based on limitations in current clinical trial methods. Furthermore, major **depressive** disorder (MDD) is a complex illness with a variety of co-occurring somatic and often **painful** symptoms. In addition, increasing evidence suggests that, in some **depressed** patients, **serotonin-norepinephrine reuptake inhibitors** (SNRIs) may provide benefits of treating a broader range of target symptoms than single-acting agents, such as selective serotonin **reuptake inhibitors** (SSRIs). Given the available evidence and the importance of remission, the pendulum has swung to consider using agents with dual **reuptake inhibition** (e.g., SNRIs) as standard and initial treatment for **depression**.

CT Acute Disease
 Adrenergic Uptake Inhibitors: TU, therapeutic use
 *Antidepressive Agents: TU, therapeutic use
 Antidepressive Agents, Tricyclic: TU, therapeutic use
 Cyclohexanols: TU, therapeutic use
 *Depressive Disorder, Major: DT, drug therapy
 Depressive Disorder, Major: PC, prevention & control
 Depressive Disorder, Major: PX, psychology
 Humans
 Placebos
 Randomized Controlled Trials
 Recurrence: PC, prevention & control

Research Support, Non-U.S. Gov't

Serotonin Uptake Inhibitors: TU, therapeutic use

Thiophenes: TU, therapeutic use

Treatment Outcome

RN 116539-58-3 (duloxetine); 93413-69-5 (venlafaxine)

CN 0 (Adrenergic Uptake Inhibitors); 0 (Antidepressive Agents); 0 (Antidepressive Agents, Tricyclic); 0 (Cyclohexanols); 0 (Placebos); 0 (Serotonin Uptake Inhibitors); 0 (Thiophenes)

L91 ANSWER 40 OF 313 MEDLINE on STN

ACCESSION NUMBER: 2003574967 MEDLINE

DOCUMENT NUMBER: PubMed ID: 14656626

TITLE: Hypertensive crisis associated with venlafaxine.

AUTHOR: Khurana Rahul N; Baudendistel Thomas E

SOURCE: American journal of medicine, (2003 Dec 1) 115 (8) 676-7.
Journal code: 0267200. ISSN: 0002-9343.

PUB. COUNTRY: United States

DOCUMENT TYPE: (CASE REPORTS)

Letter

LANGUAGE: English

FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals

ENTRY MONTH: 200401

ENTRY DATE: Entered STN: 20031216

Last Updated on STN: 20040109

Entered Medline: 20040108

CT Adult

Alcohol Deterrents: AE, adverse effects

Alcohol Deterrents: TU, therapeutic use

Alcoholism: CO, complications

Alcoholism: DT, drug therapy

***Antidepressive Agents, Second-Generation: AE, adverse effects**

Anxiety Disorders: CO, complications

Anxiety Disorders: DT, drug therapy

*Cyclohexanols: AE, adverse effects

Depression: CO, complications

Depression: DT, drug therapy

Disulfiram: AE, adverse effects

Disulfiram: TU, therapeutic use

Drug Interactions

Humans

*Hypertension: CI, chemically induced

Hypertension: CO, complications

Hypertension: DI, diagnosis

Hypertension: TH, therapy

RN 93413-69-5 (venlafaxine); 97-77-8 (Disulfiram)

CN 0 (Alcohol Deterrents); 0 (Antidepressive Agents, Second-Generation); 0 (Cyclohexanols)

L91 ANSWER 41 OF 313 MEDLINE on STN

ACCESSION NUMBER: 2003481620 MEDLINE

DOCUMENT NUMBER: PubMed ID: 14558878

TITLE: Mirtazapine-induced hyponatraemia.

AUTHOR: Roxanas Milton G

SOURCE: Medical journal of Australia, (2003 Oct 20) 179 (8) 453-4.
Journal code: 0400714. ISSN: 0025-729X.

PUB. COUNTRY: Australia

DOCUMENT TYPE: (CASE REPORTS)

Letter

LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 200401
 ENTRY DATE: Entered STN: 20031016
 Last Updated on STN: 20040109
 Entered Medline: 20040108

CT Check Tags: Female

Aged

Aged, 80 and over

Antidepressive Agents, Second-Generation: TU, therapeutic use

***Antidepressive Agents, Tricyclic: AE, adverse effects**

Cyclohexanols: AE, adverse effects

***Depression: DT, drug therapy**

Humans

Hyponatremia: BL, blood

*Hyponatremia: CI, chemically induced

Hyponatremia: UR, urine

*Mianserin: AE, adverse effects

*Mianserin: AA, analogs & derivatives

Mianserin: TU, therapeutic use

RN 24219-97-4 (Mianserin); 61337-67-5 (mirtazapine); 93413-69-5
 (venlafaxine)

CN 0 (Antidepressive Agents, Second-Generation); 0 (Antidepressive Agents,
 Tricyclic); 0 (Cyclohexanols)

L91 ANSWER 42 OF 313 MEDLINE on STN

ACCESSION NUMBER: 2003359827 MEDLINE

DOCUMENT NUMBER: PubMed ID: 12892015

TITLE: [Withdrawal symptoms in a neonate following exposure to
 venlafaxine during pregnancy].
 Onthoudingsverschijnselen bij een neonatus na blootstelling
 aan venlafaxine tijdens de zwangerschap.

COMMENT: Comment in: Ned Tijdschr Geneesk. 2003 Sep
 20;147(38):1885-6; author reply 1886. PubMed ID: 14533505

AUTHOR: de Moor R A; Mourad L; ter Haar J; Egberts A C

CORPORATE SOURCE: Afd. Kindergeneeskunde, TweeSteden ziekenhuis, Postbus
 90.107, 5000 LA Tilburg.. rdmoor@tsz.nl

SOURCE: Nederlands tijdschrift voor geneeskunde, (2003 Jul 12) 147
 (28) 1370-2.

Journal code: 0400770. ISSN: 0028-2162.

PUB. COUNTRY: Netherlands

DOCUMENT TYPE: (CASE REPORTS)

Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: Dutch

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200310

ENTRY DATE: Entered STN: 20030802
 Last Updated on STN: 20031008
 Entered Medline: 20031006

AB Withdrawal symptoms occurred in a male neonate after maternal use of
 venlafaxine for depression during pregnancy. The symptoms were
 restlessness, hypertonia, jitteriness, irritability and poor feeding. The
 diagnosis was confirmed by a temporary improvement after administration of
 a low dose (1 mg) of venlafaxine to the boy. Eventually the symptoms
 began to decline spontaneously, and ceased after 8 days. Exposure to
 venlafaxine and other antidepressants which inhibit serotonin reuptake
 during the third trimester of pregnancy carries the risk of a neonatal
 withdrawal syndrome.

CT Check Tags: Female; Male

*Antidepressive Agents, Second-Generation: AE, adverse effects
 Antidepressive Agents, Second-Generation: TU, therapeutic use
 *Cyclohexanols: AE, adverse effects
 Cyclohexanols: TU, therapeutic use
 Depression: DT, drug therapy
 English Abstract
 Humans
 Infant, Newborn
 *Neonatal Abstinence Syndrome
 Pregnancy
 Pregnancy Complications: DT, drug therapy
 *Serotonin Uptake Inhibitors: AE, adverse effects
 Serotonin Uptake Inhibitors: TU, therapeutic use

RN 93413-69-5 (venlafaxine)

CN 0 (Antidepressive Agents, Second-Generation); 0 (Cyclohexanols); 0
 (Serotonin Uptake Inhibitors)

L91 ANSWER 43 OF 313 MEDLINE on STN

ACCESSION NUMBER: 2003401032 MEDLINE

DOCUMENT NUMBER: PubMed ID: 12939435

TITLE: Risperidone-responsive segmental dystonia and pallidal deep brain stimulation.

AUTHOR: Wohrle J C; Weigel R; Grips E; Blahak C; Capelle H H; Krauss J K

CORPORATE SOURCE: Departments of Neurology, Universitätsklinikum, Mannheim, Germany.. woehrle@neuro.ma.uni-heidelberg.de

SOURCE: Neurology, (2003 Aug 26) 61 (4) 546-8.
Journal code: 0401060. ISSN: 1526-632X.

PUB. COUNTRY: United States

DOCUMENT TYPE: (CASE REPORTS)
Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals

ENTRY MONTH: 200401

ENTRY DATE: Entered STN: 20030827
Last Updated on STN: 20040130
Entered Medline: 20040129

AB A 67-year-old man with risperidone-responsive segmental dystonia underwent bilateral deep brain stimulation (DBS) of the globus pallidus internus. Prospectively, the authors assessed the Burke-Fahn-Marsden Dystonia Rating Scale in medication (M) and stimulation (S) "on"/"off" states. With DBS at 9 months, the score improved by 86% to 8.5 in M-"on"/S-"on" and 12.5 in M-"off"/S-"on." Studies of the effects of DBS and concomitant medication may be warranted in selected patients treated by DBS for dystonia.

CT Check Tags: Male

Aged

Antidepressive Agents: TU, therapeutic use

Combined Modality Therapy

Cyclohexanols: TU, therapeutic use

Depression: CI, chemically induced

Depression: DT, drug therapy

Dopamine Antagonists: AE, adverse effects

*Dopamine Antagonists: TU, therapeutic use

Dystonic Disorders: DT, drug therapy

Dystonic Disorders: PP, physiopathology

*Dystonic Disorders: TH, therapy

*Electric Stimulation Therapy

*Globus Pallidus: PP, physiopathology

Humans

Parkinson Disease, Secondary: CI, chemically induced
Risperidone: AE, adverse effects
*Risperidone: TU, therapeutic use
Severity of Illness Index

RN 106266-06-2 (Risperidone); 93413-69-5 (venlafaxine)
CN 0 (Antidepressive Agents); 0 (Cyclohexanols); 0 (Dopamine Antagonists)

L91 ANSWER 44 OF 313 MEDLINE on STN
ACCESSION NUMBER: 2003433773 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12975715
TITLE: Efficacy of venlafaxine for the long term treatment of
chronic **pain** with associated major
depressive disorder.
AUTHOR: Bradley Ronald H; Barkin Robert L; Jerome John; DeYoung
Kevin; Dodge Charles William
CORPORATE SOURCE: Total Health Care of Michigan, P.C., East Lansing, MI
48823, USA.. rhbradley@msn.com
SOURCE: American journal of therapeutics, (2003 Sep-Oct) 10 (5)
318-23.
Journal code: 9441347. ISSN: 1075-2765.
PUB. COUNTRY: United States
DOCUMENT TYPE: (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200402
ENTRY DATE: Entered STN: 20030917
Last Updated on STN: 20040207
Entered Medline: 20040206

AB BACKGROUND: This was an open-label, single-center study of the long-term
efficacy and effectiveness of venlafaxine extended release (XR) in the
treatment of chronic **pain** and **depression** in
outpatients. All patients have been diagnosed with major
depressive disorder (MDD) of various types, with or without
chronic **pain**, and had previously failed treatment with either
tricyclic **antidepressants** (TCAs) or selective serotonin
reuptake inhibitors (SSRIs). METHODS: Efficacy of
treatment was determined using the 21-item Hamilton Rating Scale for
Depression (HAMD-21), the Visual Analogue Scale (VAS) for the
evaluation of **pain**, and a 12-item quality of life scale (QOL).
Patients were treated in an unblended open trial for 1 year with 150 mg or
more of venlafaxine XR once daily. RESULTS: After 1 year of treatment,
21-item Hamilton Rating Scale for **Depression**, Visual Analogue
Scale, and quality of life scores were significantly improved from
permanent baseline scores. CONCLUSION: These data show long-term efficacy
and effectiveness of venlafaxine XR, a **serotonin** (5-HT) and
norepinephrine (NE) and dopamine (DA) **reuptake**
inhibitor antidepressant agent, having analgesic
properties.

CT Check Tags: Female; Male
Adult
Analgesics: AD, administration & dosage
*Analgesics: TU, therapeutic use
**Antidepressive Agents, Second-Generation: AD, administration &
dosage**
***Antidepressive Agents, Second-Generation: TU, therapeutic use**
Chronic Disease
Cyclohexanols: AD, administration & dosage
*Cyclohexanols: TU, therapeutic use

Delayed-Action Preparations

Depressive Disorder, Major: CO, complications

*Depressive Disorder, Major: DT, drug therapy

Humans

Pain: CO, complications

*Pain: DT, drug therapy

Pain Measurement

Serotonin Uptake Inhibitors: AD, administration & dosage

*Serotonin Uptake Inhibitors: TU, therapeutic use

Severity of Illness Index

Time Factors

Treatment Outcome

RN 93413-69-5 (venlafaxine)

CN 0 (Analgesics); 0 (Antidepressive Agents, Second-Generation); 0
 (Cyclohexanols); 0 (Delayed-Action Preparations); 0 (Serotonin
 Uptake Inhibitors)

L91 ANSWER 45 OF 313 MEDLINE on STN

ACCESSION NUMBER: 2003391337 MEDLINE

DOCUMENT NUMBER: PubMed ID: 12928711

TITLE: Therapeutic effects of milnacipran (serotonin noradrenalin
 reuptake inhibitor) on depression following mild and
 moderate traumatic brain injury.

AUTHOR: Kanetani Kouichi; Kimura Mahito; Endo Shunkichi

CORPORATE SOURCE: Department of Neuropsychiatry, Nippon Medical School,
 Tokyo, Japan.. kanetani@k6.dion.ne.jp

SOURCE: Journal of Nippon Medical School = Nihon Ika Daigaku
 zasshi, (2003 Aug) 70 (4) 313-20.
 Journal code: 100935589. ISSN: 1345-4676.

PUB. COUNTRY: Japan

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200310

ENTRY DATE: Entered STN: 20030821

Last Updated on STN: 20031018

Entered Medline: 20031017

AB BACKGROUND: The present study investigated the efficacy and safety of
 milnacipran, a serotonin noradrenalin reuptake inhibitor (SNRI), for the
 treatment of depression following mild and moderate traumatic brain injury
 (MMTBI). While other reports have been published on the use of
 antidepressants such as selective serotonin reuptake inhibitors (SSRIs)
 and tricyclics for the treatment of depression following MMTBI, no
 previous study has examined the use of a SNRI for this condition.
 METHODS: A six-week open study was conducted using 10 patients (4 males
 and 6 females) of ages ranging from 28 to 74 years. DSM-IV (diagnostic
 statistical manual of mental disorders, 4th Ed. American psychiatric
 association, 1994) was used to diagnose mood disorders. The severity of
 depression was measured with the 21-item Hamilton rating scale for
 depression (HAM-D). The cognitive state of the patients was assessed
 using the mini-mental state examination (MMSE). RESULTS: The maximum
 daily milnacipran dosage for the patients ranged from 30 to 150 mg. One
 patient experienced side effects, but none of the side effects were
 serious. On the basis of having a decrease in a final HAM-D score of more
 than 50%, the response rate for the nine patients was 66.7%, while in a
 final score of 7 or less, the remission rate for the nine patients was
 44.4%. Furthermore, significantly greater improvement in cognitive
 function was seen in patients treated with milnacipran. CONCLUSION: The
 results demonstrated that milnacipran is a safe and effective drug for

depression following mild and moderate TBI and could be the first choice drug for the treatment of this condition.

CT Check Tags: Female; Male
 *Adrenergic Uptake Inhibitors: TU, therapeutic use
 Adult
 Aged
 *Antidepressive Agents: TU, therapeutic use
 *Brain Injuries: CO, complications
 *Cyclopropanes: TU, therapeutic use
 *Depression: DT, drug therapy
 Depression: ET, etiology
 Drug Evaluation
 Humans
 Middle Aged
 *Serotonin Uptake Inhibitors: TU, therapeutic use
 RN 92623-85-3 (milnacipran)
 CN 0 (Adrenergic Uptake Inhibitors); 0 (Antidepressive Agents); 0 (Cyclopropanes); 0 (Serotonin Uptake Inhibitors)

L91 ANSWER 46 OF 313 MEDLINE on STN
 ACCESSION NUMBER: 2003249791 MEDLINE
 DOCUMENT NUMBER: PubMed ID: 12773276
 TITLE: Management of fibromyalgia.
 AUTHOR: Patkar Ashwin A; Bilal Louai; Masand Prakash S
 CORPORATE SOURCE: Department of Psychiatry, Thomas Jefferson University, 833 Chestnut Street, Suite 210E, Philadelphia, PA 19107, USA.. ashwin.patkar@mail.tju.edu
 SOURCE: Current psychiatry reports, (2003 Jul) 5 (3) 218-24. Ref: 62
 Journal code: 100888960. ISSN: 1523-3812.
 PUB. COUNTRY: United States
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
 General Review; (REVIEW)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 200401
 ENTRY DATE: Entered STN: 20030530
 Last Updated on STN: 20040117
 Entered Medline: 20040116

AB Fibromyalgia is characterized by widespread **pain**, persistent fatigue, nonrestorative sleep, and generalized morning stiffness. The diagnosis is based on patients' reports of **pain** and fatigue, clinical findings of multiple tender points, and exclusion of a range of connective tissue and other medical disorders. Treatment of fibromyalgia is multidisciplinary with an emphasis on active patient participation, medications, cognitive behavioral therapy, and physical modalities. No single medication has been found to effectively control all the symptoms, and a rational combination of different medications is often necessary. Currently available medication classes include the selective **serotonin uptake inhibitors**, the **serotonin and norepinephrine reuptake inhibitors**, tricyclic antidepressants, analgesics, hypnotic agents, and anticonvulsants. Treatment modalities should be individualized for patients based on target symptoms and impairment in functioning. As is the case with several chronic disorders, the treatment is often prolonged and improvement may occur slowly. Patience and positive attitude on part of the physician and active involvement of patients and their families in treatment are likely to enhance improvement.

CT Combined Modality Therapy
*Fibromyalgia: DI, diagnosis
Fibromyalgia: ET, etiology
Fibromyalgia: TH, therapy
Humans

Pain Measurement
Patient Care Team
Patient Participation
Prognosis

L91 ANSWER 47 OF 313 MEDLINE on STN
ACCESSION NUMBER: 2004125192 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15017493
TITLE: Effects of venlafaxine, buspirone, and placebo on colonic
sensorimotor functions in healthy humans.
AUTHOR: Chial Heather J; Camilleri Michael; Ferber Irene;
Delgado-Aros Silvia; Burton Duane; McKinzie Sanna;
Zinsmeister Alan R
CORPORATE SOURCE: Clinical Enteric Neuroscience Translational and
Epidemiological Research (C.E.N.T.E.R.) Program, Mayo
Clinic, Rochester, Minnesota 55905, USA.
CONTRACT NUMBER: K24-DK02638 (NIDDK)
R01-DK54681 (NIDDK)
RR00585 (NCRR)
SOURCE: Clin Gastroenterol Hepatol, (2003 May) 1 (3) 211-8.
Journal code: 101160775. ISSN: 1542-3565.
PUB. COUNTRY: United States
DOCUMENT TYPE: (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(RANDOMIZED CONTROLLED TRIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200404
ENTRY DATE: Entered STN: 20040313
Last Updated on STN: 20040402
Entered Medline: 20040401
AB BACKGROUND & AIMS: We have shown that venlafaxine-XR, a **serotonin**
(5-HT) and **norepinephrine reuptake inhibitor**
, enhanced gastric accommodation, whereas buspirone, a 5-HT(1A) receptor
agonist, reduced postprandial symptoms after a fully satiating meal. Our
aim was to compare the effects of venlafaxine, buspirone, and placebo on
colonic sensorimotor functions in healthy adults. METHODS: In this
randomized, double-blind, parallel-group, placebo-controlled trial of 60
healthy adults, we assessed the effects of oral venlafaxine, 150 mg;
buspirone, 20 mg; and placebo on colonic sensorimotor functions. RESULTS:
Venlafaxine increased colonic compliance relative to placebo; thus it
decreased the intracolonic balloon pressure at half-maximum volume (P =
0.001) and altered the overall shape of the compliance curve, beta (P =
0.01). Venlafaxine also decreased fasting colonic tone (P = 0.02) and the
tonic response to a meal (P = 0.003) compared with placebo; no differences
in high amplitude phasic contractile events were observed. Pressure
thresholds for first sensation (P = 0.1) and gas (P = 0.07) were not
statistically significant with venlafaxine. The increase in **pain**
scores per unit pressure during phasic distentions were affected by
treatment (P = 0.02), with smallest changes on venlafaxine and highest on
placebo. Buspirone did not significantly alter colonic compliance, tone,
or sensation relative to placebo. CONCLUSIONS: Venlafaxine alters colonic
compliance and tone, and tends to reduce sensation during colonic
distention in healthy humans. These data support the need for further

clinical and physiologic studies of venlafaxine in colonic disorders affecting motor and possibly sensory functions.

CT Check Tags: Female; Male

Adult

*Anti-Anxiety Agents: PD, pharmacology

***Antidepressive Agents, Second-Generation: PD, pharmacology**

*Buspirone: PD, pharmacology

Colon: DE, drug effects

Colon: IR, innervation

*Colon: PH, physiology

Compliance

*Cyclohexanols: PD, pharmacology

Double-Blind Method

Fasting

Humans

Pain

Postprandial Period

Pressure

Reference Values

Research Support, U.S. Gov't, P.H.S.

Sensory Thresholds

*Serotonin Agonists: PD, pharmacology

***Serotonin Uptake Inhibitors: PD, pharmacology**

RN 36505-84-7 (Buspirone); 93413-69-5 (venlafaxine)

CN 0 (Anti-Anxiety Agents); 0 (**Antidepressive Agents, Second-Generation**); 0 (Cyclohexanols); 0 (Serotonin Agonists); 0 (Serotonin **Uptake Inhibitors**)

L91 ANSWER 48 OF 313 MEDLINE on STN

ACCESSION NUMBER: 2003036985 MEDLINE

DOCUMENT NUMBER: PubMed ID: 12544554

TITLE: Diffusion of new generation antidepressant treatment among elderly diagnosed with depression.

AUTHOR: Sambamoorthi Usha; Olfson Mark; Walkup James T; Crystal Stephen

CORPORATE SOURCE: Institute for Health, Health Care Policy, and Aging Research, Rutgers University, New Brunswick, New Jersey 08901, USA.. sambamoo@rci.rutgers.edu

CONTRACT NUMBER: P20HS11825 (AHCPR)

P30 MH 43450 (NIMH)

R01 MH60831 (NIMH)

R03 AG 15166 (NIA)

R03HS09566 (AHCPR)

SOURCE: Medical care, (2003 Jan) 41 (1) 180-94.
Journal code: 0230027. ISSN: 0025-7079.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200302

ENTRY DATE: Entered STN: 20030125

Last Updated on STN: 20030208

Entered Medline: 20030207

AB RESEARCH OBJECTIVE: This study analyzes the prevalence of new generation antidepressant treatment including selective serotonin reuptake inhibitor (SSRI) use from 1992 to 1997 among the elderly diagnosed with depression, using a large, nationally representative survey of Medicare beneficiaries. Relationships between use of new generation antidepressant treatment and socioeconomic characteristics, physical comorbidity, insurance coverage,

and care sector (mental health specialty vs. general health services) are explored. RESEARCH DESIGN: Merged survey data, Medicare claims, and detailed self-reports from the Medicare Current Beneficiary Survey were used to explore use of new generation antidepressant treatment. SUBJECTS: Medicare beneficiaries aged 65 and older living in the community, enrolled in fee-for-service Medicare throughout the year and diagnosed with depression. RESULTS: In 1997, among an estimated 1.1 million community dwelling older adults with diagnosis of depression in health care claims, nearly two thirds received antidepressant treatments. Among those diagnosed with depression and treated with antidepressants, the use of new generation antidepressants increased from 35% in 1992 to 77% in 1997. The rates of use increased among all subgroups examined. In the early years after the introduction of these new antidepressant medications (1992-1994), there were socioeconomic disparities in use of these medications, with less use by less educated and poor patients. However, these differences abated over time. CONCLUSIONS: An increasing proportion of elderly treated for depression with antidepressants received the new generation antidepressants. The diffusion of these new medications lagged for those with low socioeconomic status defined by education and income. This diffusion process conforms to a general model of diffusion in which during the initial years following introduction of a new treatment, especially one which is costly, early adopters of the treatment are likely to disproportionately represent those of higher socioeconomic status.

CT Check Tags: Comparative Study; Female; Male

Age Factors

Aged

*Antidepressive Agents: TU, therapeutic use

Antidepressive Agents, Second-Generation: TU, therapeutic use

Antidepressive Agents, Tricyclic: TU, therapeutic use

Comorbidity

Continental Population Groups

Cyclohexanols: TU, therapeutic use

Depression: DI, diagnosis

*Depression: DT, drug therapy

Depression: EP, epidemiology

Diabetes Mellitus: EP, epidemiology

Fee-for-Service Plans

Health Status

Heart Diseases: EP, epidemiology

Humans

Hypertension: EP, epidemiology

Medicare

Monoamine Oxidase Inhibitors: TU, therapeutic use

Multivariate Analysis

Research Support, U.S. Gov't, P.H.S.

Sample Size

Sampling Studies

Serotonin Uptake Inhibitors: TU, therapeutic use

Sex Factors

Socioeconomic Factors

RN 93413-69-5 (venlafaxine)

CN 0 (Antidepressive Agents); 0 (Antidepressive Agents, Second-Generation); 0 (Antidepressive Agents, Tricyclic); 0 (Cyclohexanols); 0 (Monoamine Oxidase Inhibitors); 0 (Serotonin Uptake Inhibitors)

L91 ANSWER 49 OF 313 MEDLINE on STN

ACCESSION NUMBER: 2003207026 MEDLINE

DOCUMENT NUMBER: PubMed ID: 12727329

TITLE: The antihyperalgesic effect of venlafaxine in diabetic rats

does not involve the opioid system.

AUTHOR: Marchand Fabien; Alloui Abdelkrim; Chapuy Eric; Hernandez Alejandro; Pelissier Teresa; Ardid Denis; Eschalier Alain

CORPORATE SOURCE: E 9904 INSERM/UdA, Laboratoire de Pharmacologie Medicale, Faculte de Medecine, 63001 Cedex 1, Clermont-Ferrand, France.

SOURCE: Neuroscience letters, (2003 May 15) 342 (1-2) 105-8.
Journal code: 7600130. ISSN: 0304-3940.

PUB. COUNTRY: Ireland

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200307

ENTRY DATE: Entered STN: 20030503
Last Updated on STN: 20030801
Entered Medline: 20030731

AB Venlafaxine (VFX) is a structurally novel **antidepressant** that **inhibits reuptake** of **serotonin** and **norepinephrine** but, unlike tricyclic **antidepressants**, has few side effects. The present work studies the antihyperalgesic effect of repeated administrations of VFX (five successive injections of 2.5, 5 or 10 mg/kg, s.c., every half-life) in diabetic rats with the paw pressure test and the effect of the opioid receptor antagonist naloxone (1 mg/kg, i.v.) because an opioidergic mechanism is usually considered to be involved in the analgesic effect of **antidepressants**. VFX induced a significant dose-dependent increase in vocalization thresholds. This effect was not reversed by naloxone. Thus, we demonstrate a clear antinociceptive effect of VFX which, unlike that of most mixed tricyclic **antidepressants**, does not involve the endogenous opioid system.

CT Check Tags: Male
*Analgesics: PD, pharmacology
Animals
*Cyclohexanols: PD, pharmacology
Diabetes Complications
Dose-Response Relationship, Drug
*Hyperalgesia: DT, drug therapy
Hyperalgesia: ET, etiology
*Naloxone: PD, pharmacology
*Narcotic Antagonists: PD, pharmacology
*Pain Threshold: DE, drug effects
Pressure
Rats
Rats, Sprague-Dawley
Research Support, Non-U.S. Gov't
Vocalization, Animal: DE, drug effects

RN 465-65-6 (Naloxone); 93413-69-5 (venlafaxine)

CN 0 (Analgesics); 0 (Cyclohexanols); 0 (Narcotic Antagonists)

L91 ANSWER 50 OF 313 MEDLINE on STN

ACCESSION NUMBER: 2003314206 MEDLINE

DOCUMENT NUMBER: PubMed ID: 12842359

TITLE: Fatal overdoses of tramadol: is benzodiazepine a risk factor of lethality?.

AUTHOR: Clarot F; Gouille J P; Vaz E; Proust B

CORPORATE SOURCE: Department of Forensic Medicine, Rouen University Hospital, CHU Rouen, Charles Nicolle, Rouen 76031, France..
frank.clarot@chu-rouen.fr

SOURCE: Forensic science international, (2003 Jun 24) 134 (1) 57-61.

Journal code: 7902034. ISSN: 0379-0738.
PUB. COUNTRY: Ireland
DOCUMENT TYPE: (CASE REPORTS)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200310
ENTRY DATE: Entered STN: 20030708
Last Updated on STN: 20031015
Entered Medline: 20031014

AB Tramadol is a centrally acting analgesic agent used in the treatment of mild to moderate pain. It has a low affinity to opioid receptors and inhibits the reuptake of norepinephrin and serotonin producing an analgesic action by blocking nociceptive impulses in the spine. Although 21 drug-combined fatalities including tramadol have been reported, only two fatal overdoses in adults with tramadol alone have been reported to date. We report four additional lethal intoxications, assess the toxicity of tramadol, the detection method and the possible interaction with other central nervous system (CNS) depressants, particularly benzodiazepines. Similarities between tramadol and buprenorphine are discussed, and a possible cytochrome P450-based interaction between tramadol and benzodiazepine is considered. To our knowledge, this relationship has never been reported in the literature.

CT Check Tags: Male
Adult
Analgesics, Opioid: CH, chemistry
*Analgesics, Opioid: PO, poisoning
Humans
Middle Aged
Molecular Structure
Overdose
Tramadol: CH, chemistry
*Tramadol: PO, poisoning

RN 27203-92-5 (Tramadol)
CN 0 (Analgesics, Opioid)

L91 ANSWER 51 OF 313 MEDLINE on STN
ACCESSION NUMBER: 2003588699 MEDLINE
DOCUMENT NUMBER: PubMed ID: 14669603
TITLE: [Experience with ixel (milnacipran hydrochloride) use in the treatment of patients with post-stroke depression].
Opyt primeneniia iksela (milnatsiprana gidrokhlorida) u bol'nykh s postinsul'tnoi depressiei.
AUTHOR: Gekht A B; Sorokina I B; Bogolepova A N; Gudkova A A
SOURCE: Terapevticheskii arkhiv, (2003) 75 (10) 34-8.
Journal code: 2984818R. ISSN: 0040-3660.
PUB. COUNTRY: Russia: Russian Federation
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: Russian
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200405
ENTRY DATE: Entered STN: 20031216
Last Updated on STN: 20040518
Entered Medline: 20040517

AB AIM: To evaluate antidepressive efficacy of ixel in patients with poststroke depression (PSD). MATERIAL AND METHODS: The study included 59 PSD patients aged 43-79 years divided into two groups: the test group (31 patients) treated with antidepressive drugs and the control group (28

patients) was not treated with such drugs. The test group took a two-month treatment with oral ixel in a dose 100 mg/day. The neurological status was assessed by Lindmark scale (LS), severity of depression-by Hamilton scale (HS). RESULTS: On ixel treatment day 10-14 the patients felt better, by the treatment day 60 depression disappeared in 60.9%, only borderline conditions were seen in 39.1%. Mean score by HS fell from 15.8 to 5.7. The controls showed moderate reduction of some symptoms of depression, mean score by HS decreased insignificantly (from 14.5 to 13.4). By LS, significant differences between the groups were not registered. Side effects arose in 10 patients, 6 of them withdrew. CONCLUSION: Ixel is an effective drug against depression in stroke survivors.

CT Check Tags: Female; Male

Adult

Aged

Antidepressive Agents: AE, adverse effects

*Antidepressive Agents: TU, therapeutic use

Case-Control Studies

*Cerebrovascular Accident: CO, complications

Cerebrovascular Accident: PX, psychology

Cyclopropanes: AE, adverse effects

*Cyclopropanes: TU, therapeutic use

*Depression: DT, drug therapy

Depression: ET, etiology

Depression: PX, psychology

English Abstract

Humans

Middle Aged

Severity of Illness Index

Treatment Outcome

RN 92623-85-3 (milnacipran)

CN 0 (Antidepressive Agents); 0 (Cyclopropanes)

L91 ANSWER 52 OF 313 MEDLINE on STN

ACCESSION NUMBER: 2003477723 MEDLINE

DOCUMENT NUMBER: PubMed ID: 14552653

TITLE: The role of the serotonergic and noradrenergic neurotransmitter systems in the treatment of psychological and physical symptoms of **depression**.

AUTHOR: Fava Maurizio

CORPORATE SOURCE: Depression Clinical and Research Program, Massachusetts General Hospital, Boston, MA 02114, USA..
Mfava@Partners.org

SOURCE: Journal of clinical psychiatry, (2003) 64 Suppl 13 26-9.
Ref: 34

Journal code: 7801243. ISSN: 0160-6689.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200401

ENTRY DATE: Entered STN: 20031015

Last Updated on STN: 20040121

Entered Medline: 20040120

AB Major **depressive** disorder is a medical condition that includes abnormalities of affect and mood, cognition, and physical functioning. In particular, as many as 76% of patients suffering from **depression**

are found to report somatic symptoms, including various types of **pain** such as headaches, stomach **pain**, back **pain**, and vague, poorly localized **pain**. Although the pathophysiology of **depression** is still unknown, there is significant evidence for abnormalities of the **norepinephrine** (NE) and **serotonin** (5-HT) neurotransmitter systems in **depressive** disorders. Interestingly, both 5-HT and NE also appear to exert analgesic effects via descending **pain** pathways and therefore play a modulating role in **pain**. There are many effective **antidepressant** treatments available. However, residual symptoms are relatively common, among both partial responders and responders without remission. A recent study from our group has shown that responders who have not achieved remission have significantly more somatic symptoms than remitters following 8 weeks of treatment with fluoxetine. These data may suggest that **antidepressants** that are particularly effective in the treatment of **pain** and painful physical symptoms may yield higher remission rates in major **depressive** disorder.

CT *Adrenergic Uptake Inhibitors: TU, therapeutic use
 *Antidepressive Agents: TU, therapeutic use
 *Depressive Disorder: DT, drug therapy
 Depressive Disorder: PP, physiopathology
 Depressive Disorder: PX, psychology
 Fluoxetine: TU, therapeutic use
 Humans
 *Norepinephrine: PH, physiology
 *Pain: DT, drug therapy
 Pain: PP, physiopathology
 Pain: PX, psychology
 Research Support, Non-U.S. Gov't
 *Serotonin: PH, physiology
 *Serotonin Uptake Inhibitors: TU, therapeutic use
 *Somatoform Disorders: DT, drug therapy
 Somatoform Disorders: PP, physiopathology
 Somatoform Disorders: PX, psychology
 Treatment Outcome
 RN 50-67-9 (Serotonin); 51-41-2 (Norepinephrine); 54910-89-3 (Fluoxetine)
 CN 0 (Adrenergic Uptake Inhibitors); 0 (Antidepressive Agents); 0 (Serotonin Uptake Inhibitors)

L91 ANSWER 53 OF 313 MEDLINE on STN
 ACCESSION NUMBER: 2003600863 MEDLINE
 DOCUMENT NUMBER: PubMed ID: 14682027
 TITLE: Physical symptoms comorbid with **depression** and the new **antidepressant** duloxetine.
 AUTHOR: Bailey Katharine P
 CORPORATE SOURCE: Yale University School of Nursing, New Haven, Connecticut, USA.. katharine.bailey@yale.edu
 SOURCE: Journal of psychosocial nursing and mental health services, (2003 Dec) 41 (12) 13-8. Ref: 33
 Journal code: 8200911. ISSN: 0279-3695.
 PUB. COUNTRY: United States
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
 General Review; (REVIEW)
 (REVIEW, TUTORIAL)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals; Nursing Journals
 ENTRY MONTH: 200401

ENTRY DATE: Entered STN: 20031220
Last Updated on STN: 20040117
Entered Medline: 20040116

AB Most general descriptions of **depression** that date back to Hippocrates, including the DSM-IV, have listed gastrointestinal problems, sleep disturbances, headaches, appetite changes, and aches and **pains** of a diffuse nature as common features of the disorder. In addition, physical symptoms have a strong association with psychiatric disorders, and the presence of any physical symptom may increase the likelihood of a mood or anxiety disorder by two-fold or three-fold. A growing body of evidence suggests that **serotonin** and **norepinephrine** may share neurochemical mechanisms that tie **depression** and physical symptoms together. Both selective serotonin **reuptake inhibitors** alone and **antidepressant** agents that incorporate both **serotonin** and **norepinephrine reuptake inhibition** have shown evidence of relieving physical symptoms. Given the additional disease burden caused by physical symptoms in **depression**, it is vital that **antidepressant** agents that effectively treat the physical symptoms and chronic **pain** associated with **depression** be used.

CT **Adrenergic Uptake Inhibitors: PD, pharmacology**
***Adrenergic Uptake Inhibitors: TU, therapeutic use**
Antidepressive Agents: PD, pharmacology
***Antidepressive Agents: TU, therapeutic use**
Anxiety Disorders
Comorbidity
***Depressive Disorder: CO, complications**
Depressive Disorder: DI, diagnosis
***Depressive Disorder: DT, drug therapy**
Depressive Disorder: PP, physiopathology
***Gastrointestinal Diseases: ET, etiology**
Gastrointestinal Diseases: PC, prevention & control
Humans
Mood Disorders
Norepinephrine: PH, physiology
***Pain: ET, etiology**
Pain: PC, prevention & control
Psychophysiologic Disorders
Serotonin: PH, physiology
Serotonin Uptake Inhibitors: PD, pharmacology
***Serotonin Uptake Inhibitors: TU, therapeutic use**
***Sleep Disorders: ET, etiology**
Sleep Disorders: PC, prevention & control
Thiophenes: PD, pharmacology
***Thiophenes: TU, therapeutic use**
Treatment Outcome
RN 116539-58-3 (duloxetine); 50-67-9 (Serotonin); 51-41-2 (Norepinephrine)
CN 0 (**Adrenergic Uptake Inhibitors**); 0 (**Antidepressive Agents**); 0 (**Serotonin Uptake Inhibitors**); 0 (**Thiophenes**)

L91 ANSWER 54 OF 313 MEDLINE on STN
ACCESSION NUMBER: 2002488649 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12325062
TITLE: Interaction between ECT and venlafaxine.
AUTHOR: Jha A; Tomar R
SOURCE: International journal of geriatric psychiatry, (2002 Oct)
17 (10) 979-80.

Journal code: 8710629. ISSN: 0885-6230.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: (CASE REPORTS)
Letter
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200211
ENTRY DATE: Entered STN: 20020927
Last Updated on STN: 20021214
Entered Medline: 20021126
CT Check Tags: Female
Aged
*Antidepressive Agents, Second-Generation: TU, therapeutic use
Antihypertensive Agents: TU, therapeutic use
Atenolol: TU, therapeutic use
Combined Modality Therapy: AE, adverse effects
*Cyclohexanols: TU, therapeutic use
*Depression: DT, drug therapy
*Electroconvulsive Therapy: MT, methods
Fatal Outcome
Humans
Hypertension: DT, drug therapy
RN 29122-68-7 (Atenolol); 93413-69-5 (venlafaxine)
CN 0 (Antidepressive Agents, Second-Generation); 0 (Antihypertensive Agents);
0 (Cyclohexanols)

L91 ANSWER 55 OF 313 MEDLINE on STN
ACCESSION NUMBER: 2002728268 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12490351
TITLE: Silent thyroiditis associated with short-term lithium therapy.
AUTHOR: Numata Shusuke; Taniguchi Kyoko; Harada Takashi; Tomotake Masahito; Ohmori Tetsuro
SOURCE: General hospital psychiatry, (2002 Nov-Dec) 24 (6) 451-3.
Journal code: 7905527. ISSN: 0163-8343.
PUB. COUNTRY: United States
DOCUMENT TYPE: (CASE REPORTS)
Letter
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200304
ENTRY DATE: Entered STN: 20021220
Last Updated on STN: 20030424
Entered Medline: 20030423

CT Check Tags: Female
Antidepressive Agents: AD, administration & dosage
*Antidepressive Agents: AE, adverse effects
Clomipramine: TU, therapeutic use
Cyclopropanes: TU, therapeutic use
*Depression: DT, drug therapy
Drug Administration Schedule
Humans
Lithium Carbonate: AD, administration & dosage
*Lithium Carbonate: AE, adverse effects
Middle Aged
*Thyroiditis: CI, chemically induced
Time Factors
RN 303-49-1 (Clomipramine); 554-13-2 (Lithium Carbonate); 92623-85-3
(milnacipran)

CN 0 (Antidepressive Agents); 0 (Cyclopropanes)

L91 ANSWER 56 OF 313 MEDLINE on STN

ACCESSION NUMBER: 2002481810 MEDLINE

DOCUMENT NUMBER: PubMed ID: 12243607

TITLE: Nefopam abuse.

AUTHOR: Villier Celine; Mallaret Michel P

CORPORATE SOURCE: Centre d'Evaluation et d'Information sur la
Pharmacodependance de Grenoble, Grenoble, France..
CVillier@chu-grenoble.fr

SOURCE: Annals of pharmacotherapy, (2002 Oct) 36 (10) 1564-6.
Journal code: 9203131. ISSN: 1060-0280.

PUB. COUNTRY: United States

DOCUMENT TYPE: (CASE REPORTS)

Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200304

ENTRY DATE: Entered STN: 20020924

Last Updated on STN: 20030426

Entered Medline: 20030425

AB OBJECTIVE: To report 3 patients who abused nefopam, a central analgesic that inhibits **serotonin**, **norepinephrine**, and dopamine reuptake. CASE SUMMARIES: CASE 1: A 42-year-old white woman with migraines started nefopam therapy about 10 years ago. She now obtains nefopam by prescription forgery and self-administers intramuscular nefopam 300 mg/d. She experiences anticholinergic effects of nefopam and, when attempting withdrawal, **depressive** symptoms. CASE 2: A 40-year-old white woman with osteoporosis has injected 120 mg of nefopam intramuscularly daily for several years. When she tried to increase doses due to worsening of her symptoms, she experienced tremor, involuntary movements, and dry mouth, and became aggressive. She then resumed the initial doses. She now reports symptoms of **depression** when attempting withdrawal. CASE 3: A 33-year-old white man, with a history of alcohol and benzodiazepine dependence and ileostomy, and an implanted drug delivery system, has been prescribed nefopam. Fifteen days after therapy was initiated, his daily consumption was 840 mg/d, and further increased to 1840 mg/d. He experienced violent behavior, agitation, facial dysesthesia and myoclonus, tremor of fingers, and sweating. He did not attempt withdrawal. DISCUSSION: The patients described above are drug-dependent according to the Diagnostic and Statistical Manual, 4th Edition. All patients developed a pharmacodynamic tolerance phenomenon, which can develop rapidly. Violent behavior, tremor after massive intake, and **depressive** symptoms during withdrawal are similar to those reported with psychostimulant abuse. CONCLUSIONS: When abused, nefopam has primarily psychostimulant-like effects, which are probably linked to its dopamine **reuptake inhibition** properties.

CT Check Tags: Female; Male

Adult

*Analgesics, Non-Narcotic: AD, administration & dosage
Humans

Injections, Intramuscular

Injections, Intravenous

*Nefopam: AD, administration & dosage

Pain: DT, drug therapy

*Substance-Related Disorders: ET, etiology

RN 13669-70-0 (Nefopam)

CN 0 (Analgesics, Non-Narcotic)

L91 ANSWER 57 OF 313 MEDLINE on STN
 ACCESSION NUMBER: 2002383983 MEDLINE
 DOCUMENT NUMBER: PubMed ID: 12132141
 TITLE: [Delirium during withdrawal of venlafaxine].
 Delirium bij afbouw van venlafaxine.
 AUTHOR: van Noorden M S; Vergouwen A C M; Koerselman G F
 CORPORATE SOURCE: Sint Lucas Andreas Ziekenhuis, afd. Psychiatrie, Postbus
 9243, 1006 AE Amsterdam.
 SOURCE: Nederlands tijdschrift voor geneeskunde, (2002 Jun 29) 146
 (26) 1236-7.
 Journal code: 0400770. ISSN: 0028-2162.
 PUB. COUNTRY: Netherlands
 DOCUMENT TYPE: (CASE REPORTS)
 Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: Dutch
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 200210
 ENTRY DATE: Entered STN: 20020723
 Last Updated on STN: 20021024
 Entered Medline: 20021023

AB A 35-year-old man with anxiety and depression who was treated with
 venlafaxine, 300 mg a day, developed severe withdrawal symptoms in the
 form of a delirium during gradual tapering of the dosage. The symptoms
 resolved when the dosage was kept constant and did not recur when the
 dosage was reduced more gradually. Withdrawal symptoms are common during
 discontinuation of antidepressants, particularly after prolonged use of
 agents with a short half-life. The symptoms are usually mild and
 transient, especially in the case of selective serotonin reuptake
 inhibitors and venlafaxine. The occurrence of delirium as a result of the
 withdrawal of venlafaxine has not been reported previously. Even when
 antidepressants are being withdrawn with care, one should remain alert to
 the possible development of severe withdrawal symptoms.

CT Check Tags: Male
 Adult

Antidepressive Agents, Second-Generation: AD, administration &
 dosage

*Antidepressive Agents, Second-Generation: AE, adverse effects

Antidepressive Agents, Second-Generation: PK, pharmacokinetics

Cyclohexanols: AD, administration & dosage

*Cyclohexanols: AE, adverse effects

Cyclohexanols: PK, pharmacokinetics

*Delirium: CI, chemically induced

Delirium: ET, etiology

Depression: DT, drug therapy

Drug Administration Schedule

English Abstract

Half-Life

Humans

Serotonin Uptake Inhibitors: AD, administration & dosage

*Serotonin Uptake Inhibitors: AE, adverse effects

Serotonin Uptake Inhibitors: PK, pharmacokinetics

*Substance Withdrawal Syndrome: PP, physiopathology

RN 93413-69-5 (venlafaxine)

CN 0 (Antidepressive Agents, Second-Generation); 0 (Cyclohexanols); 0
 (Serotonin Uptake Inhibitors)

L91 ANSWER 58 OF 313 MEDLINE on STN
 ACCESSION NUMBER: 2002430137 MEDLINE
 DOCUMENT NUMBER: PubMed ID: 12187335

TITLE: Dramatic recovery of paclitaxel-disabling neurosensory toxicity following treatment with venlafaxine.
 AUTHOR: Durand Jean-Philippe; Goldwasser Francois
 CORPORATE SOURCE: Unite d'Oncologie Medicale, Service de Medecine Interne 1, Groupe Hospitalier Cochin, AP-HP, 75679 Paris, France.
 SOURCE: Anti-cancer drugs, (2002 Aug) 13 (7) 777-80.
 Journal code: 9100823. ISSN: 0959-4973.
 PUB. COUNTRY: England: United Kingdom
 DOCUMENT TYPE: (CASE REPORTS)
 Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 200302
 ENTRY DATE: Entered STN: 20020821
 Last Updated on STN: 20030206
 Entered Medline: 20030205

AB Venlafaxine is an **antidepressant** which acts through the **inhibition** of the **reuptake** of **norepinephrine** and **serotonin**. Venlafaxine is active against neuropathic and chronic **pain**. We report the case of a 69-year-old woman who presented a paclitaxel-induced neuropathy. She presented paresthesias, pin pricks in both hands with functional impairment. Venlafaxine hydrochloride was introduced at 37.5 mg twice daily. The patient noticed a dramatic recovery of her symptoms within 2 days, with both reduction of the paresthesias and functional improvement. This is the first report of efficacious use of venlafaxine for the treatment of paclitaxel cumulative neurosensory toxicity.

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CT Check Tags: Female
 Adenocarcinoma: CO, complications
 Adenocarcinoma: DT, drug therapy
 Aged
 *Antidepressive Agents, Second-Generation: TU, therapeutic use
 *Antineoplastic Agents, Phytogenic: AE, adverse effects
 *Cyclohexanols: TU, therapeutic use
 Humans
 *Neurotoxicity Syndromes: DT, drug therapy
 Ovarian Neoplasms: CO, complications
 Ovarian Neoplasms: DT, drug therapy
 *Paclitaxel: AE, adverse effects
 Paresthesia: CI, chemically induced
 Paresthesia: DT, drug therapy
 Sensation Disorders: CI, chemically induced
 *Sensation Disorders: DT, drug therapy
 RN 33069-62-4 (Paclitaxel); 93413-69-5 (venlafaxine)
 CN 0 (**Antidepressive** Agents, Second-Generation); 0 (Antineoplastic Agents, Phytogenic); 0 (Cyclohexanols)

L91 ANSWER 59 OF 313 MEDLINE on STN
 ACCESSION NUMBER: 2002716503 MEDLINE
 DOCUMENT NUMBER: PubMed ID: 12429415
 TITLE: In the rat forced swimming test, chronic but not subacute administration of dual 5-HT/NA antidepressant treatments may produce greater effects than selective drugs.
 AUTHOR: Reneric Jean-Philippe; Bouvard Manuel; Stinus Luis
 CORPORATE SOURCE: Laboratoire de Neuropsychobiologie des Desadaptations, Centre National de la Recherche Scientifique, Unite Mixte de Recherche 5541, BP31, Universite Bordeaux II, 33076 Bordeaux Cedex, France.. jean-philippe.renic@labopsy.u-

SOURCE: brodeaux2.fr
 Behavioural brain research, (2002 Nov 15) 136 (2) 521-32.
 Journal code: 8004872. ISSN: 0166-4328.
 PUB. COUNTRY: Netherlands
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 200301
 ENTRY DATE: Entered STN: 20021218
 Last Updated on STN: 20030204
 Entered Medline: 20030121

AB The rat forced swimming test (FST) distinguishes selective serotonin (5-HT) and selective noradrenaline (NA) reuptake-inhibitors, which respectively increase swimming and climbing behaviours. However, NA-system-mediated inhibition of 5-HT-induced swimming prevents dual 5-HT/NA reuptake-inhibition to produce concurrently climbing with swimming. Since adaptative neurochemical processes occur in the treatment of depression, we examined the influence of long-term antidepressant treatment on these interactions. METHODS: (1) Selective [fluoxetine: 10 mg/kg; desipramine: 10 mg/kg] and non-selective [milnacipran: 40 mg/kg; mirtazapine: 20 mg/kg] antidepressants were administered subacutely (3inj) and chronically (17inj) over 16 days. (2) A subacute fluoxetine-desipramine combination (10-10 mg/kg) was administered in rats that were pre-treated with chronic-desipramine (10 mg/kg per day, 14 days). (3) NA-system-mediated interactions were further examined by combining the alpha(2)-receptor agonist clonidine (5, 10, 20, 200 microg/kg) with 10 mg/kg fluoxetine. RESULTS: (1) Long-term treatment with either fluoxetine or desipramine does not modify the behavioural response produced by their subacute administration. (2) In contrast, whereas subacute-milnacipran increases climbing solely, chronic-milnacipran produces greater anti-immobility effects and increases both climbing and swimming behaviours. Similarly, the fluoxetine-desipramine combination produces climbing solely, but increases both climbing and swimming behaviours in animals pre-treated with chronic-desipramine. Chronic but not subacute-mirtazapine increases swimming behaviour. (3) clonidine dose-dependently antagonizes fluoxetine-induced anti-immobility effects and swimming behaviour. CONCLUSIONS: Chronic enhancement of NA-transmission alters NA-system-mediated inhibition of 5-HT-induced behaviour in the FST, which may involve alpha(2)-receptors. Copyright 2002 Elsevier Science B.V.

CT Check Tags: Male
 *Adrenergic Uptake Inhibitors: TU, therapeutic use
 Adrenergic alpha-Agonists: PD, pharmacology
 Animals
 *Antidepressive Agents, Second-Generation: TU, therapeutic use
 *Behavior, Animal: DE, drug effects
 Clonidine: PD, pharmacology
 Cyclopropanes: TU, therapeutic use
 *Depression: DT, drug therapy
 *Depression: PX, psychology
 Desipramine: TU, therapeutic use
 Dose-Response Relationship, Drug
 Drug Synergism
 Fluoxetine: TU, therapeutic use
 *Mianserin: AA, analogs & derivatives
 Mianserin: TU, therapeutic use
 Motor Activity: DE, drug effects
 *Norepinephrine: PH, physiology
 Rats

Rats, Sprague-Dawley
 Receptors, Adrenergic, alpha-2: DE, drug effects
 Research Support, Non-U.S. Gov't

*Serotonin Uptake Inhibitors: TU, therapeutic use

*Swimming: PX, psychology

RN 24219-97-4 (Mianserin); 4205-90-7 (Clonidine); 50-47-5 (Desipramine);
 51-41-2 (Norepinephrine); 54910-89-3 (Fluoxetine); 61337-67-5

(mirtazapine); **92623-85-3 (milnacipran)**

CN 0 (Adrenergic Uptake Inhibitors); 0 (Adrenergic alpha-Agonists); 0
 (Antidepressive Agents, Second-Generation); 0 (Cyclopropanes); 0
 (Receptors, Adrenergic, alpha-2); 0 (Serotonin Uptake Inhibitors)

L91 ANSWER 60 OF 313 MEDLINE on STN

ACCESSION NUMBER: 2002311798 MEDLINE

DOCUMENT NUMBER: PubMed ID: 12054096

TITLE: **Antidepressants** in pain management.

AUTHOR: Carter Gregory T; Sullivan Mark D

CORPORATE SOURCE: Department of Rehabilitation Medicine, University of
 Washington School of Medicine, Seattle 98195, USA..
 gtcarter@u.washington.edu

SOURCE: Current opinion in investigational drugs (London, England :
 2000), (2002 Mar) 3 (3) 454-8. Ref: 59
 Journal code: 100965718. ISSN: 1472-4472.

PUB. COUNTRY: England: United Kingdom

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
 General Review; (REVIEW)
 (REVIEW, TUTORIAL)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200211

ENTRY DATE: Entered STN: 20020611
 Last Updated on STN: 20021211
 Entered Medline: 20021122

AB **Antidepressants** exhibit a number of pharmacological mechanisms,
 including **norepinephrine** and **serotonin** modulation,
 direct and indirect effects on opioid receptors, inhibition of histamine,
 cholinergic and N-methyl-D-aspartate receptors, and inhibition of ion
 channel activity. Although it is not entirely clear which mechanisms
 produce analgesia and to what extent, the available animal and clinical
 trials data indicates that tricyclic **antidepressants** are
 effective in treating many types of **pain**. The newer selective
 serotonin **reuptake inhibitors** also appear to be
 effective for chronic headache and other non-neuropathic forms of chronic
pain but are not as well studied. This article reviews the
 current basic and clinical research on **antidepressants** in
pain management.

CT Animals

***Antidepressive Agents**: TU, therapeutic use

Chronic Disease

Headache: DT, drug therapy

Headache: PP, physiopathology

Humans

***Pain**: DT, drug therapy

Pain: ET, etiology

Pain: PX, psychology

Peripheral Nervous System Diseases: CO, complications

Peripheral Nervous System Diseases: PX, psychology

Research Support, U.S. Gov't, Non-P.H.S.

CN 0 (**Antidepressive Agents**)

L91 ANSWER 61 OF 313 MEDLINE on STN
ACCESSION NUMBER: 2002635523 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12393307
TITLE: Duloxetine 60 mg once daily dosing versus placebo in the acute treatment of major **depression**.
AUTHOR: Detke Michael J; Lu Yili; Goldstein David J; McNamara Robert K; Demitrack Mark A
CORPORATE SOURCE: Lilly Research Laboratories, Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN, USA..
detke_michael@lilly.com
SOURCE: Journal of psychiatric research, (2002 Nov-Dec) 36 (6) 383-90.
Journal code: 0376331. ISSN: 0022-3956.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(MULTICENTER STUDY)
(RANDOMIZED CONTROLLED TRIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200303
ENTRY DATE: Entered STN: 20021024
Last Updated on STN: 20030322
Entered Medline: 20030321
AB Existing therapies for major **depressive** disorder (MDD) have either limited efficacy and/or poor tolerability. The present study examined the effects of duloxetine, a potent and balanced dual **reuptake inhibitor** of **serotonin** (5-HT) and **norepinephrine** (NE), in patients with MDD. Adult patients (N = 267) with MDD were randomly assigned to receive duloxetine (60 mg/day) or placebo in this 9-week, multi-center, double-blind, parallel-group clinical trial. Efficacy was evaluated using the 17-item Hamilton **Depression** Rating Scale (HAM-D(17)), Visual Analog Scales (VAS) for **pain**, Clinical Global Impression of Severity (CGI-S), Patient's Global Impression of Improvement (PGI-I), and Quality of Life in **Depression** Scale (QLDS). Safety was evaluated by assessing discontinuation rates, adverse event rates, vital signs, and laboratory tests. Duloxetine (60 mg QD) significantly reduced the HAM-D(17) total score compared with placebo at the end of 9-week therapy. Estimated probabilities of response and remission were 65 and 43%, respectively, for duloxetine compared with 42 and 28% for placebo. Duloxetine also reduced overall **pain**, back **pain**, shoulder **pain** and time in **pain** while awake significantly more than placebo. Global measures of improvement, including PGI-I and QLDS, were significantly improved by duloxetine compared with placebo. Discontinuations due to adverse events were more frequent for duloxetine-treated patients (12.5%) than for placebo-treated patients (4.3%). Nausea, dry mouth, dizziness, and constipation were more frequent for duloxetine than placebo. There was no significant incidence of hypertension, nor any other safety issues. Duloxetine 60 mg administered once daily appears to be a safe and effective treatment for MDD. Copyright 2002 Elsevier Science Ltd.
CT Check Tags: Female; Male
Adult
Antidepressive Agents: AD, administration & dosage
Antidepressive Agents: AE, adverse effects
*Antidepressive Agents: TU, therapeutic use
Depressive Disorder, Major: DI, diagnosis

***Depressive Disorder, Major: DT, drug therapy**
Double-Blind Method
Drug Administration Schedule
Humans
Severity of Illness Index
Thiophenes: AD, administration & dosage
Thiophenes: AE, adverse effects
*Thiophenes: TU, therapeutic use
Treatment Outcome

RN 116539-58-3 (duloxetine)

CN 0 (**Antidepressive Agents**); 0 (Thiophenes)

L91 ANSWER 62 OF 313 MEDLINE on STN

ACCESSION NUMBER: 2002350157 MEDLINE

DOCUMENT NUMBER: PubMed ID: 12093597

TITLE: Effects of acute and chronic reboxetine treatment on stress-induced monoamine efflux in the rat frontal cortex.

AUTHOR: Page Michelle E; Lucki Irwin

CORPORATE SOURCE: Department of Psychiatry, University of Pennsylvania, 538 Clinical Research Building, 415 Curie Boulevard, Philadelphia, PA 19104, USA.. page@drexel.edu

CONTRACT NUMBER: MH61418 (NIMH)

SOURCE: Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology, (2002 Aug) 27 (2) 237-47.

Journal code: 8904907. ISSN: 0893-133X.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200208

ENTRY DATE: Entered STN: 20020703

Last Updated on STN: 20020808

Entered Medline: 20020807

AB Reboxetine is a selective noradrenergic **reuptake inhibitor** that displays an **antidepressant** profile in both animal tests and in clinical trials. The present study examined the ability of reboxetine to alter stress-induced increases in **norepinephrine**, **serotonin** and dopamine efflux in the frontal cortex in awake behaving rats. Acute systemic administration of reboxetine (0.3-20.0 mg/kg) dose-dependently increased extracellular norepinephrine in the frontal cortex while having no effect on extracellular serotonin. At 20 mg/kg, reboxetine also increased extracellular dopamine. Application of a 20-min tailpinch stress increased extracellular norepinephrine. This effect was greatly potentiated in rats pretreated with reboxetine. Tailpinch did not elicit increases in dopamine in saline treated animals but this stimulus increased dopamine levels following reboxetine pretreatment. Furthermore, chronic administration of reboxetine for 14 days resulted in elevated basal concentrations of extracellular norepinephrine and dopamine and a greater net increase of extracellular **norepinephrine** and dopamine, but not **serotonin**, in response to tailpinch compared with vehicle control animals. Taken together, these data support the view that the noradrenergic and dopaminergic systems are modified by reboxetine treatment and may be important factors in the mechanism of action of **antidepressant** compounds.

CT Check Tags: Male

***Adrenergic Uptake Inhibitors: PD, pharmacology**
Adrenergic alpha-Agonists: PD, pharmacology

Animals

Antidepressive Agents: PD, pharmacology

*Biogenic Monoamines: ME, metabolism

Clonidine: PD, pharmacology

Dopamine: ME, metabolism

Dopamine: SE, secretion

Dose-Response Relationship, Drug

Drug Administration Schedule

Extracellular Space: DE, drug effects

Extracellular Space: ME, metabolism

Microdialysis

*Morpholines: PD, pharmacology

Neural Pathways: DE, drug effects

Neural Pathways: ME, metabolism

Neural Pathways: PP, physiopathology

Norepinephrine: ME, metabolism

Norepinephrine: SE, secretion

Pain Threshold: DE, drug effects**Pain Threshold: PH, physiology**

Physical Stimulation: AE, adverse effects

*Prefrontal Cortex: DE, drug effects

Prefrontal Cortex: ME, metabolism

Prefrontal Cortex: PP, physiopathology

*Presynaptic Terminals: DE, drug effects

Presynaptic Terminals: ME, metabolism

Rats

Rats, Sprague-Dawley

Receptors, Adrenergic, alpha-2: DE, drug effects

Receptors, Adrenergic, alpha-2: ME, metabolism

Research Support, Non-U.S. Gov't

Research Support, U.S. Gov't, P.H.S.

Serotonin: ME, metabolism

Serotonin: SE, secretion

*Stress: DT, drug therapy

Stress: ME, metabolism

Stress: PP, physiopathology

*Synaptic Transmission: DE, drug effects

Synaptic Transmission: PH, physiology

RN 4205-90-7 (Clonidine); 50-67-9 (Serotonin); 51-41-2 (Norepinephrine);
51-61-6 (Dopamine); 98769-81-4 (reboxetine)CN 0 (Adrenergic Uptake Inhibitors); 0 (Adrenergic
alpha-Agonists); 0 (Antidepressive Agents); 0 (Biogenic
Monoamines); 0 (Morpholines); 0 (Receptors, Adrenergic, alpha-2)

L91 ANSWER 63 OF 313 MEDLINE on STN

ACCESSION NUMBER: 2002345732 MEDLINE

DOCUMENT NUMBER: PubMed ID: 12088962

TITLE: An investigation of monoamine receptors involved in
antinociceptive effects of antidepressants.AUTHOR: Yokogawa Fumiko; Kiuchi Yuji; Ishikawa Yuji; Otsuka Naoki;
Masuda Yutaka; Oguchi Katsuji; Hosoyamada AkiyoshiCORPORATE SOURCE: Department of Anesthesiology, School of Medicine, Showa
University, 1-5-8 Hatanodai, Shinagawa-ku, Tokyo 142-8666,
Japan.. yokogawa@jz8.so-net.ne.jpSOURCE: Anesthesia and analgesia, (2002 Jul) 95 (1) 163-8, table of
contents.

Journal code: 1310650. ISSN: 0003-2999.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English
 FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
 ENTRY MONTH: 200207
 ENTRY DATE: Entered STN: 20020629
 Last Updated on STN: 20020724
 Entered Medline: 20020723

AB We attempted to determine which monoamine receptor subtypes are predominantly involved in **antidepressant**-induced antinociception. Antinociceptive effects were evaluated by using formalin tests with rats. **Antidepressants** acting as potent **inhibitors** of norepinephrine **reuptake** (nisoxetine, nortriptyline, and maprotiline) or **inhibiting reuptake** of both **norepinephrine** and **serotonin** (5-HT) (imipramine and milnacipran) induced dose-dependent antinociception. Simultaneous intraperitoneal administration of **antidepressants** and either prazosin (alpha(1) antagonist) or ketanserin (5-HT(2) antagonist) significantly antagonized antinociceptive effects. Fluvoxamine (selective serotonin **reuptake inhibitor**) induced antinociception less potently than other **antidepressants** and was significantly antagonized by ketanserin, but not prazosin. Ondansetron (5-HT(3) antagonist) significantly antagonized antinociception by 10 mg/kg of imipramine. In contrast, SDZ-205,557 (5-HT(4) antagonist) markedly enhanced antinociception by small-dose (2.5 mg/kg) imipramine. Imipramine-induced antinociception was significantly antagonized by intracerebroventricular administration of prazosin or ketanserin, but not by yohimbine (alpha(2) antagonist) or ondansetron, and was significantly enhanced by intracerebroventricularly administered SDZ-205,557. These findings suggest that alpha(1) adrenoceptors and 5-HT(2) receptors in the brain are involved in **antidepressant**-induced antinociception. In addition, the results suggested functional interactions between noradrenergic and serotonergic neurons as mechanisms for **antidepressant**-induced antinociception. IMPLICATIONS: Formalin tests of rats treated with **antidepressants** and antagonists of monoamine receptors indicate that alpha(1) adrenoceptors, serotonin (5-HT)(2) receptors, and 5-HT(3) receptors are involved in **antidepressant**-induced antinociception, suggesting functional interactions between noradrenergic and serotonergic neurons as mechanisms of **antidepressant**-induced antinociception.

CT Check Tags: Male

Adrenergic alpha-Antagonists: PD, pharmacology

*Analgesics

Animals

Antidepressive Agents: AI, antagonists & inhibitors

***Antidepressive Agents: PD, pharmacology**

Dose-Response Relationship, Drug

Formaldehyde: DU, diagnostic use

Injections, Intraperitoneal

Injections, Intraventricular

Motor Activity: DE, drug effects

Norepinephrine: PH, physiology

Pain Measurement: DE, drug effects

Rats

Rats, Wistar

Receptor, Serotonin, 5-HT2A

Receptors, Adrenergic, alpha-1: AI, antagonists & inhibitors

Receptors, Adrenergic, alpha-1: DE, drug effects

Receptors, Adrenergic, alpha-2: AI, antagonists & inhibitors

Receptors, Adrenergic, alpha-2: DE, drug effects

Receptors, Biogenic Amine: AI, antagonists & inhibitors

*Receptors, Biogenic Amine: DE, drug effects

Receptors, Serotonin: DE, drug effects

Receptors, Serotonin, 5-HT3

Receptors, Serotonin, 5-HT4

Serotonin Antagonists: PD, pharmacology

RN 158165-40-3 (Receptors, Serotonin, 5-HT4); 50-00-0 (Formaldehyde); 51-41-2 (Norepinephrine)

CN 0 (Adrenergic alpha-Antagonists); 0 (Analgesics); 0 (Antidepressive Agents); 0 (Receptor, Serotonin, 5-HT2A); 0 (Receptors, Adrenergic, alpha-1); 0 (Receptors, Adrenergic, alpha-2); 0 (Receptors, Biogenic Amine); 0 (Receptors, Serotonin); 0 (Receptors, Serotonin, 5-HT3); 0 (Serotonin Antagonists)

L91 ANSWER 64 OF 313 MEDLINE on STN

ACCESSION NUMBER: 2002728780 IN-PROCESS

DOCUMENT NUMBER: PubMed ID: 12490826

TITLE: Coping with somatic comorbidities: striving for complete recovery.

AUTHOR: Allgulander Christer; Kasper Siegfried

CORPORATE SOURCE: Karolinska Institute, Neurotec Department, Huddinge University Hospital, Stockholm, Sweden..

Allgulander@neurotec.ki.se

SOURCE: Psychopharmacology bulletin, (2002 Summer) 36 Suppl 2 103-11.

Journal code: 0101123. ISSN: 0048-5764.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: NONMEDLINE; IN-DATA-REVIEW; IN-PROCESS; NONINDEXED; Priority Journals

ENTRY DATE: Entered STN: 20021220

Last Updated on STN: 20031217

AB **Depression** is increasingly being recognized as a common comorbid disorder in patients with severe and chronic medical conditions. However, patients with **depression** and anxiety frequently present with somatic complaints such as aches and **pains**, headache, and chronic fatigue. This leads to underrecognition and undertreatment of the psychiatric disorder in an attempt to identify the medical cause of the somatic complaint. Reports are demonstrating the efficacy of **antidepressants** in treating disorders other than **depression** and anxiety. Tricyclic **antidepressants** have shown their usefulness in the treatment of diabetic neuropathy, fibromyalgia, and headache. Controlled studies of several selective serotonin **reuptake inhibitors** have been shown to be efficacious in relieving the symptoms of premenstrual dysphoric disorder and fibromyalgia. Pilot studies have also been conducted with the **serotonin and norepinephrine reuptake inhibitor** venlafaxine for the treatment of diabetic neuropathy, fibromyalgia, migraine, premenstrual dysphoric disorder, and stroke. The results encourage further controlled studies.

L91 ANSWER 65 OF 313 MEDLINE on STN

ACCESSION NUMBER: 2002196266 MEDLINE

DOCUMENT NUMBER: PubMed ID: 11928783

TITLE: Treatment of psychotic depression associated with steroid therapy in Churg-Strauss syndrome.

AUTHOR: Ismail M; Lyster G

CORPORATE SOURCE: St Brigid's Hospital, Ardee, Co Louth..
drismail@ireland.com

SOURCE: Irish medical journal, (2002 Jan) 95 (1) 18-9.
Journal code: 0430275. ISSN: 0332-3102.

PUB. COUNTRY: Ireland

DOCUMENT TYPE: (CASE REPORTS)
Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200204

ENTRY DATE: Entered STN: 20020404
Last Updated on STN: 20020418
Entered Medline: 20020417

AB A case of depressive psychosis associated with corticosteroid therapy for the treatment of Churg-Strauss syndrome is described. We outline the patient's response to different antidepressant and antipsychotic medications in this case. A significant improvement with low doses of Venlafaxine is open for further discussion and study.

CT Check Tags: Female
*Adrenal Cortex Hormones: AE, adverse effects
Adrenal Cortex Hormones: TU, therapeutic use
Antidepressive Agents, Second-Generation: TU, therapeutic use
Antipsychotic Agents: TU, therapeutic use
*Churg-Strauss Syndrome: DT, drug therapy
Cyclohexanols: TU, therapeutic use
***Depression: CI, chemically induced**
Depression: TH, therapy
Electroconvulsive Therapy
Humans
Middle Aged
Paroxetine: TU, therapeutic use
Risperidone: TU, therapeutic use

RN 106266-06-2 (Risperidone); 61869-08-7 (Paroxetine); **93413-69-5 (venlafaxine)**

CN 0 (Adrenal Cortex Hormones); 0 (Antidepressive Agents, Second-Generation);
0 (Antipsychotic Agents); 0 (Cyclohexanols)

L91 ANSWER 66 OF 313 MEDLINE on STN

ACCESSION NUMBER: 2002263141 MEDLINE

DOCUMENT NUMBER: PubMed ID: 12003058

TITLE: Can improvement in well-being and functioning be distinguished from depression improvement in antidepressant clinical trials?.

AUTHOR: Pedersen Ronald D; Pallay Allan G; Rudolph Richard L

CORPORATE SOURCE: Wyeth-Ayerst Research, Radnor, Philadelphia, Pennsylvania 19101, USA... pedersr@war.wyeth.com

SOURCE: Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation, (2002 Feb) 11 (1) 9-17.
Journal code: 9210257. ISSN: 0962-9343.

PUB. COUNTRY: Netherlands

DOCUMENT TYPE: (CLINICAL TRIAL)
(CONTROLLED CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200206

ENTRY DATE: Entered STN: 20020511
Last Updated on STN: 20020620
Entered Medline: 20020619

AB The Inventory of General Life Functioning (GLF), a self-evaluation scale

for patients, was developed for use in the National Institute of Mental Health Treatment of Depression Collaborative Research Program. The scale was designed to evaluate patient general well-being and functioning, areas not adequately covered by standard depression scales. We used the patient self-report version of the GLF in two imipramine-controlled clinical trials during the development of the antidepressant venlafaxine. In these double-blind studies, outpatients with depression received placebo (n = 158), venlafaxine (n = 152), or imipramine (n = 149) for up to 6 weeks. We examined the internal consistency and factor structure of the GLF, its correlation with standard depression rating scales, and its sensitivity to differential treatment effects. We found the scale to be internally consistent and moderately correlated with physician-rated measures of depression. A reported two-factor structure (general well-being and functioning) was evaluated by factor analysis. When analyses were restricted to patients who completed at least 4 weeks on therapy, the GLF displayed sensitivity to differential treatment effects. The GLF total and factor subscales demonstrated the superiority of an active therapy (venlafaxine) to placebo; the GLF factor and a 7-item subscale using only items derived from Dupuy's psychological general well-being index (PGWB) demonstrated an advantage for one active therapy (venlafaxine) over another (imipramine). The GLF is a useful complement to the standard depression rating scales because it may assess additional dimensions of the depressive syndrome.

CT Check Tags: Female; Male

*Activities of Daily Living

Adult

Analysis of Variance

*Antidepressive Agents, Second-Generation: TU, therapeutic use

*Antidepressive Agents, Tricyclic: TU, therapeutic use

Controlled Clinical Trials

*Cyclohexanols: TU, therapeutic use

*Depression: DT, drug therapy

*Depression: PX, psychology

Factor Analysis, Statistical

Humans

*Imipramine: TU, therapeutic use

*Outcome Assessment (Health Care): MT, methods

*Psychiatric Status Rating Scales

Psychometrics

Reproducibility of Results

RN 50-49-7 (Imipramine); 93413-69-5 (venlafaxine)

CN 0 (Antidepressive Agents, Second-Generation); 0 (Antidepressive Agents, Tricyclic); 0 (Cyclohexanols)

L91 ANSWER 67 OF 313 MEDLINE on STN

ACCESSION NUMBER: 2001651392 MEDLINE

DOCUMENT NUMBER: PubMed ID: 11704162

TITLE: Venlafaxine in the treatment of premenstrual dysphoric disorder.

AUTHOR: Freeman E W; Rickels K; Yonkers K A; Kunz N R; McPherson M; Upton G V

CORPORATE SOURCE: Department of Obstetrics/Gynecology, School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania 19104, USA.. freemane@mail.med.upenn.edu

SOURCE: Obstetrics and gynecology, (2001 Nov) 98 (5 Pt 1) 737-44. Journal code: 0401101. ISSN: 0029-7844.

PUB. COUNTRY: United States

DOCUMENT TYPE: (CLINICAL TRIAL)

Journal; Article; (JOURNAL ARTICLE)

(MULTICENTER STUDY)
(RANDOMIZED CONTROLLED TRIAL)

LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200112
ENTRY DATE: Entered STN: 20011114
Last Updated on STN: 20020123
Entered Medline: 20011205

AB OBJECTIVE: To evaluate the efficacy and safety of venlafaxine, a new-generation **antidepressant** that selectively **inhibits serotonin and norepinephrine reuptake**, in the treatment of premenstrual dysphoric disorder (PMDD). METHOD: We conducted a randomized, double-blind, placebo-controlled, parallel-group, flexible-dose trial. After three screening cycles, including a single-blind placebo cycle, 164 women were randomly assigned to double-blind treatment with venlafaxine (50-200 mg/day) or placebo for four menstrual cycles. Primary outcome measures were the total premenstrual symptom scores as assessed by a daily symptom report (DSR) and the Hamilton Rating Scale for **Depression**. RESULTS: Venlafaxine was significantly more effective than placebo in reducing PMDD symptoms as assessed by DSR scores ($P < .001$ for last observation carried forward and observed analyses). Sixty percent of venlafaxine versus 35% of placebo subjects improved $>50\%$ ($P = .003$). Forty-three percent of venlafaxine subjects versus 25% of placebo subjects experienced symptom remission, defined as reduction of DSR scores to the postmenstrual level ($P = .034$). Venlafaxine treatment was significantly better than placebo for all statistically derived DSR factors (mood, function, **pain**, and physical symptoms). Improvement was relatively swift, with approximately 80% symptom reduction in the first treatment cycle. Mean venlafaxine doses ranged from 50 mg/day in the first treatment cycle to 130 mg/day in the fourth treatment cycle. Adverse events such as nausea, insomnia, and dizziness were mild and transient. CONCLUSIONS: Venlafaxine is significantly more efficacious than placebo for PMDD treatment. Response to treatment can occur in the first treatment cycle, and venlafaxine is well tolerated. Further studies are needed to evaluate the potential of intermittent (luteal phase) dosing for this cyclic disorder and the efficacy of long-term maintenance treatment with venlafaxine.

CT Check Tags: Female
Adult
*Cyclohexanols: TU, therapeutic use
Double-Blind Method
Humans
Premenstrual Syndrome: DI, diagnosis
*Premenstrual Syndrome: DT, drug therapy
Psychiatric Status Rating Scales
Research Support, Non-U.S. Gov't
*Serotonin Uptake Inhibitors: TU, therapeutic use
RN 93413-69-5 (venlafaxine)
CN 0 (Cyclohexanols); 0 (Serotonin Uptake Inhibitors)

L91 ANSWER 68 OF 313 MEDLINE on STN
ACCESSION NUMBER: 2001523238 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11570029
TITLE: The pharmacoeconomics of venlafaxine in depression.
AUTHOR: Morrow T J
SOURCE: American journal of managed care, (2001 Sep) 7 (11 Suppl)
S386-92. Ref: 19
Journal code: 9613960. ISSN: 1088-0224.
PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
 General Review; (REVIEW)
 (REVIEW, TUTORIAL)

LANGUAGE: English

FILE SEGMENT: Health

ENTRY MONTH: 200111

ENTRY DATE: Entered STN: 20010926

Last Updated on STN: 20011105

Entered Medline: 20011101

AB The prevalence of depression and the high costs associated with its management have heightened interest in pharmacoeconomic evaluation of drug treatment, especially the use of selective serotonin reuptake inhibitors (SSRIs) and the serotonin-norepinephrine reuptake inhibitor venlafaxine. A number of studies of venlafaxine in both inpatient and outpatient settings have revealed that extended-release venlafaxine has a lower expected cost than comparable treatment with SSRIs and tricyclic antidepressants (TCAs). When the relative cost effectiveness of immediate-release venlafaxine, SSRIs, and TCAs was assessed in the treatment of major depressive disorder in 10 countries, venlafaxine yielded a lower than expected cost compared with SSRIs and TCAs in all but 1 country. In comparing healthcare expenditures for depressed patients with and without anxiety, there was a pharmacoeconomic benefit to both immediate- or extended-release venlafaxine, regardless of the presence or absence of comorbid anxiety. A review of computerized administrative claims data from 9 US healthcare plans on resource use and the cost of venlafaxine instead of TCAs after switching from an SSRI showed that overall costs did not vary markedly between venlafaxine and TCAs. This led to the conclusion that although therapy with venlafaxine is more costly than TCA therapy, this increase may be offset by lower costs of other medical services. Such findings have enormous potential ramifications for practicing physicians in terms of venlafaxine's superior remission rate, lower likelihood of relapse, loss of fewer patients to adverse events or lack of efficacy, and flexibility in dosing that enables titration to achieve an optimal response.

CT Check Tags: Comparative Study

*Antidepressive Agents, Second-Generation: EC, economics

*Antidepressive Agents, Second-Generation: TU, therapeutic use

Antidepressive Agents, Tricyclic: EC, economics

Antidepressive Agents, Tricyclic: TU, therapeutic use

Anxiety: CO, complications

Anxiety: EC, economics

Cost-Benefit Analysis

*Cyclohexanols: EC, economics

*Cyclohexanols: TU, therapeutic use

Depression: CO, complications

*Depression: DT, drug therapy

Depression: EC, economics

Drug Utilization Review

Humans

Managed Care Programs: EC, economics

Managed Care Programs: OG, organization & administration

Serotonin Uptake Inhibitors: EC, economics

Serotonin Uptake Inhibitors: TU, therapeutic use

United States

RN 93413-69-5 (venlafaxine)

CN 0 (Antidepressive Agents, Second-Generation); 0 (Antidepressive Agents, Tricyclic); 0 (Cyclohexanols); 0 (Serotonin Uptake Inhibitors)

L91 ANSWER 69 OF 313 MEDLINE on STN

ACCESSION NUMBER: 2002004210 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11752890
TITLE: The reductions in sweetened milk intake induced by interleukin-1 and endotoxin are not prevented by chronic antidepressant treatment.
AUTHOR: Dunn A J; Swiergiel A H
CORPORATE SOURCE: Department of Pharmacology and Therapeutics, Louisiana State University Health Sciences Center, Shreveport, LA 71130-3932, USA.. adunn@lsuhsc.edu
CONTRACT NUMBER: NS35370 (NINDS)
SOURCE: Neuroimmunomodulation, (2001) 9 (3) 163-9.
Journal code: 9422763. ISSN: 1021-7401.
PUB. COUNTRY: Switzerland
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200202
ENTRY DATE: Entered STN: 20020102
Last Updated on STN: 20020222
Entered Medline: 20020221

AB Administration of interleukin-1 (IL-1) and endotoxin (lipopolysaccharide, LPS) to rodents can decrease food intake, a behavioral response resembling the diminution of appetite observed in human depression. IL-1 and LPS are known to affect cerebral neurotransmission involving norepinephrine and serotonin, both of which have been implicated in feeding behavior and in the pharmacotherapy of depression in man. The ability of chronic antidepressant treatment to attenuate LPS-induced depressed feeding in rats has been cited as evidence that cytokines may be involved in human depression. Thus, we studied the effects of chronic treatment with the tricyclic antidepressant, imipramine, and the novel antidepressant, venlafaxine, on the sweetened milk intake challenged with intraperitoneally injected IL-1 beta and LPS. Chronic (from 2 to 8 weeks) treatment of the mice with imipramine (10 mg/kg once or twice daily) or venlafaxine (10 and 20 mg/kg/day) did not significantly alter the decreases in milk intake in response to mIL-1 beta or LPS. In some experiments, chronic imipramine slightly decreased body weight and slightly increased milk intake, but not food pellet intake. Venlafaxine had none of these effects. Analysis of variance did not indicate any significant interactions between the antidepressant and IL-1 or LPS treatments. These results indicate that chronic treatment with antidepressants does not significantly alter the responses to IL-1 or LPS in the mouse sweetened milk model of sickness behavior.
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CT Check Tags: Male
Adrenergic Uptake Inhibitors: PD, pharmacology
Animals
Antidepressive Agents: IM, immunology
***Antidepressive Agents: PD, pharmacology**
*Appetite: DE, drug effects
Appetite: IM, immunology
Body Weight: DE, drug effects
Body Weight: IM, immunology
Brain: DE, drug effects
Brain: IM, immunology
Brain: ME, metabolism
Cyclohexanols: PD, pharmacology
Depression: DT, drug therapy
***Depression: IM, immunology**
Depression: ME, metabolism

Dose-Response Relationship, Drug
Drug Administration Schedule

*Eating: DE, drug effects

Eating: IM, immunology

Imipramine: PD, pharmacology

Interleukin-1: IM, immunology

*Interleukin-1: PD, pharmacology

Lipopolysaccharides: IM, immunology

Lipopolysaccharides: PD, pharmacology

Mice

Milk: ME, metabolism

*Neuroimmunomodulation: DE, drug effects

Neuroimmunomodulation: PH, physiology

Norepinephrine: ME, metabolism

Research Support, U.S. Gov't, P.H.S.

Serotonin: ME, metabolism

Serotonin Uptake Inhibitors: PD, pharmacology

RN 50-49-7 (Imipramine); 50-67-9 (Serotonin); 51-41-2 (Norepinephrine);

93413-69-5 (venlafaxine)

CN 0 (Adrenergic Uptake Inhibitors); 0 (Antidepressive Agents); 0
(Cyclohexanols); 0 (Interleukin-1); 0 (Lipopolysaccharides); 0 (Serotonin
Uptake Inhibitors)

L91 ANSWER 70 OF 313 MEDLINE on STN

ACCESSION NUMBER: 2001369809 MEDLINE

DOCUMENT NUMBER: PubMed ID: 11296311

TITLE: Prefrontal changes and treatment response prediction in
depression.

AUTHOR: Cook I A; Leuchter A F

CORPORATE SOURCE: Quantitative EEG Laboratory and Clinical Neurophysiology
Program, Department of Psychiatry and Biobehavioral
Sciences, Neuropsychiatric Institute and Hospital, UCLA
School of Medicine, Los Angeles, CA, USA.. icook@ucla.edu

CONTRACT NUMBER: K02-MH01165 (NIMH)

R01-MH40705 (NIMH)

SOURCE: Seminars in clinical neuropsychiatry, (2001 Apr) 6 (2)
113-20.

Journal code: 9604647. ISSN: 1084-3612.

PUB. COUNTRY: United States

DOCUMENT TYPE: (CASE REPORTS)

Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200106

ENTRY DATE: Entered STN: 20010702

Last Updated on STN: 20010702

Entered Medline: 20010628

AB A continuing challenge in the treatment of depression is how to determine
whether an effective drug has been selected for a particular patient,
given that individuals will respond to some antidepressants but not
others. The factors that contribute to response for each person have been
examined from a variety of perspectives, both psychological and
physiological. Advances in neuroimaging and in quantitative
electroencephalography (QEEG) have made it possible to examine features of
brain activity that are associated with response. A new QEEG measure,
cordance, is correlated with regional cortical perfusion, and has been
used with retrospective and prospective studies to evaluate specific
findings that are predictive of clinical response in major depression. We
present here a series of depressed subjects treated with antidepressants

of different classes; decreases in prefrontal activity were seen as early as 48 hours into treatment in responders and were absent in nonresponders. These findings suggest a role for the prefrontal region in mediating response to medications with different mechanisms of action and raise the possibility of using new QEEG measures to identify changes in brain activity that are predictive of clinical outcome from antidepressant treatment.

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CT Check Tags: Comparative Study; Female; Male
Adult

***Antidepressive Agents: TU, therapeutic use**

Cyclohexanols: TU, therapeutic use

Depression: DT, drug therapy

Depression: PP, physiopathology

*Depressive Disorder, Major: DT, drug therapy

*Depressive Disorder, Major: PP, physiopathology

*Electroencephalography: DE, drug effects

Fluoxetine: TU, therapeutic use

Humans

Middle Aged

Paroxetine: TU, therapeutic use

*Prefrontal Cortex: DE, drug effects

Prefrontal Cortex: PP, physiopathology

Research Support, Non-U.S. Gov't

Research Support, U.S. Gov't, P.H.S.

Sertraline: TU, therapeutic use

RN 54910-89-3 (Fluoxetine); 61869-08-7 (Paroxetine); 79617-96-2 (Sertraline);
93413-69-5 (venlafaxine)

CN 0 (Antidepressive Agents); 0 (Cyclohexanols)

L91 ANSWER 71 OF 313 MEDLINE on STN

ACCESSION NUMBER: 2001417046 MEDLINE

DOCUMENT NUMBER: PubMed ID: 11466159

TITLE: Symptom reduction and suicide risk in patients treated with placebo in antidepressant clinical trials: a replication analysis of the Food and Drug Administration Database.

COMMENT: Comment in: Int J Neuropsychopharmacol. 2001 Dec;4(4):447.
PubMed ID: 11811161

Comment in: Int J Neuropsychopharmacol. 2002

Mar;5(1):107-8. PubMed ID: 12057036

AUTHOR: Khan A; Khan S R; Leventhal R M; Brown W A

CORPORATE SOURCE: The Northwest Clinical Research Center, Bellevue, WA, USA..
arif@accessone.com

SOURCE: international journal of neuropsychopharmacology / official scientific journal of the Collegium Internationale Neuropsychopharmacologicum (CINP), (2001 Jun) 4 (2) 113-8.
Journal code: 9815893. ISSN: 1461-1457.

PUB. COUNTRY: England: United Kingdom

DOCUMENT TYPE: (CLINICAL TRIAL)

(CONTROLLED CLINICAL TRIAL)

Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200108

ENTRY DATE: Entered STN: 20010820

Last Updated on STN: 20020626

Entered Medline: 20010816

AB The assumption that depressed patients who are assigned to placebo in antidepressant clinical trials are exposed to substantial morbidity and

mortality has not been based on research data. Because of worldwide concern about placebo use and the implications of our earlier findings of no increased suicide risk in placebo-treated patients, we conducted a replication study in a new patient sample. We assessed suicide risk and symptom reduction among placebo-treated patients participating in antidepressant clinical trials for two recently approved antidepressants, venlafaxine ER and citalopram, which were unavailable during our previous study. Among 23,201 participant patients, 32 committed suicide and 172 attempted suicide. Rates of suicide and attempted suicide did not differ significantly among the placebo- and drug-treated groups. Based on patient exposure years, annual rates of suicide and attempted suicide were 0.5 and 6.7% with placebo, 0.9% with active comparator (rates for attempted suicide are unavailable), and 0.6 and 6.3% with investigational antidepressants. Symptom reduction was 47.9% with investigational drugs (n = 1172), 47.5% with active comparators (n = 161), and 35.5% with placebo (n = 606). These data may inform discussions about the use of placebo in antidepressant clinical trials.

CT Check Tags: Female; Male

Adult

Aged

*Antidepressive Agents, Second-Generation: TU, therapeutic use

*Citalopram: TU, therapeutic use

*Cyclohexanols: TU, therapeutic use

Databases, Factual

*Depression: DT, drug therapy

*Depression: EP, epidemiology

Follow-Up Studies

Humans

Incidence

Middle Aged

Risk

*Serotonin Uptake Inhibitors: TU, therapeutic use

Suicide: PC, prevention & control

*Suicide: PX, psychology

*Suicide: SN, statistics & numerical data

Suicide, Attempted: PX, psychology

Suicide, Attempted: SN, statistics & numerical data

United States: EP, epidemiology

United States Food and Drug Administration

RN 59729-33-8 (Citalopram); 93413-69-5 (venlafaxine)

CN 0 (Antidepressive Agents, Second-Generation); 0 (Cyclohexanols); 0 (Serotonin Uptake Inhibitors)

L91 ANSWER 72 OF 313 MEDLINE on STN

ACCESSION NUMBER: 2002203555 MEDLINE

DOCUMENT NUMBER: PubMed ID: 11935666

TITLE: [Family physician's interventions and prescribing practice. Results of the GAD-P study].
Hausarztliche Interventionen und Verschreibungsverhalten.
Ergebnisse der GAD-P-Studie.

AUTHOR: Wittchen H U; Hoyer J; Hofler M; Krause P

CORPORATE SOURCE: Institut fur Klinische Psychologie und Psychotherapie,
Technische Universitat Dresden und Max-Planck-Institut fur
Psychiatrie, Munchen.

SOURCE: Fortschritte der Medizin. Originalien, (2001) 119 Suppl 1
36-41.

Journal code: 101120496.

PUB. COUNTRY: Germany: Germany, Federal Republic of

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: German
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 200205
 ENTRY DATE: Entered STN: 20020409
 Last Updated on STN: 20020507
 Entered Medline: 20020506

AB More than two thirds of all GAD patients are recognized as cases with mental disorders, only one third is correctly diagnosed. The paper shows that this has significant implications. 36%--as compared to 23% of those with major depression--receive no intervention. Of those recognized at least as a case the majority is treated by the GP, 9% are only referred to specialists, in addition to another 20% that are treated by the GP and referred as well. Almost all patients receive medication, however, only few medications that match scientific guidelines for GAD-specific treatments, namely SNRI, behavioural psychotherapy or SSRI. Also the high degree of comedication as well as high prescription rates for sedatives and phytotonics needs highlighting. The findings overall reveal an unsatisfactory picture of current treatment strategies for GAD patients in primary--especially if compared to depression. Treatments of first choice, SNRI (Venlafaxine SR) and behavioural psychotherapy are prescribed to only the minority of GAD sufferers.

CT Check Tags: Comparative Study; Female; Male

Antidepressive Agents, Second-Generation: TU, therapeutic use
 Antipsychotic Agents: TU, therapeutic use
 Anxiety Disorders: CO, complications
 Anxiety Disorders: DT, drug therapy
 *Anxiety Disorders: TH, therapy
 Barbiturates: TU, therapeutic use
 Behavior Therapy
 Cyclohexanols: TU, therapeutic use
Depression: CO, complications
Depression: DT, drug therapy
***Depression: TH, therapy**
 English Abstract
 Humans
 Hypnotics and Sedatives: TU, therapeutic use
 *Physicians, Family
 Phytotherapy
 Referral and Consultation
 Research Support, Non-U.S. Gov't
 Serotonin Uptake Inhibitors: TU, therapeutic use

RN 93413-69-5 (venlafaxine)

CN 0 (Antidepressive Agents, Second-Generation); 0 (Antipsychotic Agents); 0 (Barbiturates); 0 (Cyclohexanols); 0 (Hypnotics and Sedatives); 0 (Serotonin Uptake Inhibitors)

L91 ANSWER 73 OF 313 MEDLINE on STN

ACCESSION NUMBER: 2001651284 MEDLINE

DOCUMENT NUMBER: PubMed ID: 11704969

TITLE: A multinational pharmacoeconomic evaluation of acute major **depressive** disorder (MDD): a comparison of cost-effectiveness between venlafaxine, SSRIs and TCAs.

AUTHOR: Doyle J J; Casciano J; Arikian S; Tarride J E; Gonzalez M A; Casciano R

CORPORATE SOURCE: Columbia University, School of Public Health, New York, NY, USA.. jdoyle@grouponalytica.com

SOURCE: Value in health : journal of the International Society for Pharmacoeconomics and Outcomes Research, (2001 Jan-Feb) 4 (1) 16-31.

Journal code: 100883818. ISSN: 1098-3015.
 PUB. COUNTRY: United States
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 200112
 ENTRY DATE: Entered STN: 20011114
 Last Updated on STN: 20020123
 Entered Medline: 20011204

AB METHODS: We conducted a multinational pharmacoeconomic evaluation comparing the immediate release form of a new class of **serotonin norepinephrine reuptake inhibitor** (SNRI), venlafaxine IR to the selective serotonin **reuptake inhibitors** (SSRIs) and the tricyclic **antidepressants** (TCAs) in the treatment of acute major **depressive** disorder (MDD) in 10 countries (Germany, Italy, Netherlands, Poland, **Spain**, Sweden, Switzerland, United Kingdom, United States, and Venezuela). We designed a decision analytic model assessing the acute phase of MDD treatment within a 6-month time horizon. Six decision tree models were customized with country-specific estimates from a clinical management analysis, meta-analytic rates from two published meta-analyses, and a resource valuation of treatment costs representing the inpatient and outpatient settings within each country. The meta-analyses provided the clinical rates of success defined as a 50% reduction in **depression** scores on the Hamilton **Depression** Scale (HAM-D) or the Montgomery-Asberg **Depression** Rating Scale (MADRS). Treatment regimen costs were determined from standard lists, fee schedules, and communication with local health economists in each country. The meta-analytic rates were applied to the decision analytic model to calculate the expected cost and expected outcomes for each **antidepressant** comparator. Cost-effectiveness was determined using the expected values for both a successful outcome, and a composite measure of outcome termed symptom-free days. A policy analysis was conducted to examine the health system budget impact in each country of increasing the utilization of the most effective **antidepressant** found in our study. RESULTS: Initiating treatment of MDD with venlafaxine IR yielded a lower expected cost compared to the SSRIs and TCAs in all countries except Poland in the inpatient setting, and Italy and Poland within the outpatient settings. The weighted average expected cost per patient varied from US\$632 (Poland) to US\$5647 (US) in the six-month acute phase treatment of MDD. The estimated total budgetary impact for each 1% of venlafaxine utilization, assuming a population of one million MDD patients, ranged from US\$1600 (Italy) to US\$29,049 (US). CONCLUSIONS: Within the inpatient and outpatient treatment settings, venlafaxine IR was a more cost-effective treatment of MDD compared to the SSRIs and TCAs. Additionally, the results of this investigation indicate that increased utilization of venlafaxine in most settings across Europe and the Americas will have favorable impact on health care payer budgets. ADR, adverse drug reaction; CMA, clinical management analysis; ECT, electroconvulsive therapy; HAM-D, Hamilton **Depression** Scale; MADRS, Montgomery-Asberg **depression** rating scale; MDD, major **depressive** disorder; SFD, symptom-free day; SNRI, **serotonin-norepinephrine reuptake inhibitor**; SSRI, selective **serotonin reuptake inhibitor**; TCA, tricyclic **antidepressant**; WHO, world health organization.

CT Check Tags: Comparative Study
 *Antidepressive Agents, Second-Generation: EC, economics
 Antidepressive Agents, Second-Generation: TU, therapeutic use

*Antidepressive Agents, Tricyclic: EC, economics
 Antidepressive Agents, Tricyclic: TU, therapeutic use
 Budgets
 Cost-Benefit Analysis
 *Cyclohexanols: EC, economics
 Cyclohexanols: TU, therapeutic use
 Decision Trees
 *Depressive Disorder, Major: DT, drug therapy
 Depressive Disorder, Major: EC, economics
 Drug Costs: SN, statistics & numerical data
 *Economics, Pharmaceutical: SN, statistics & numerical data
 Europe
 Health Services Research: MT, methods
 Humans
 Insurance, Health, Reimbursement
 Monte Carlo Method
 Research Support, Non-U.S. Gov't
 *Serotonin Uptake Inhibitors: EC, economics
 Serotonin Uptake Inhibitors: TU, therapeutic use
 United States
 Venezuela

RN 93413-69-5 (venlafaxine)

CN 0 (Antidepressive Agents, Second-Generation); 0 (
 Antidepressive Agents, Tricyclic); 0 (Cyclohexanols); 0 (Serotonin
 Uptake Inhibitors)

L91 ANSWER 74 OF 313 MEDLINE on STN

ACCESSION NUMBER: 2001056233 MEDLINE

DOCUMENT NUMBER: PubMed ID: 10940096

TITLE: Venlafaxine extended release (XR) for the prophylaxis of
 migraine and tension-type headache: A retrospective study
 in a clinical setting.

AUTHOR: Adelman L C; Adelman J U; Von Seggern R; Mannix L K

CORPORATE SOURCE: Headache Wellness Center, Greensboro, NC 27403, USA.

SOURCE: Headache, (2000 Jul-Aug) 40 (7) 572-80.
 Journal code: 2985091R. ISSN: 0017-8748.

PUB. COUNTRY: United States

DOCUMENT TYPE: (CLINICAL TRIAL)
 Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200012

ENTRY DATE: Entered STN: 20010322
 Last Updated on STN: 20010322
 Entered Medline: 20001221

AB OBJECTIVE: To assess the efficacy of extended-release venlafaxine in the
 prophylaxis of migraine and chronic tension-type headache. BACKGROUND:
 Venlafaxine, a structurally novel **antidepressant**, is a selective
**serotonin-norepinephrine reuptake
 inhibitor**. This study is the first to test the effects of
 extended-release venlafaxine on headaches. METHODS: Patients were
 evaluated on a retrospective basis. Fifty-six patients with chronic
 tension-type headache and 114 patients with migraine were prescribed
 extended-release venlafaxine. Nearly all the study subjects had been
 resistant to several previous preventive medications. Patients took
 venlafaxine for an average of 6 months with a median dose of 150 mg
 (range, 37.5 to 300 mg). RESULTS: The mean frequency of headaches in the
 group with chronic tension-type headache fell from 24.0 to 15.2 per month
 (P <.0001). The group with migraine showed a reduction from 16.1 to 11.1

headaches per month ($P < .0001$). The medicine was well tolerated.
 CONCLUSIONS: This trial indicates that extended-release venlafaxine has potential in headache prophylaxis based on its efficacy and safety profile. We recommend a double-blind, placebo-controlled study to further assess the role of extended-release venlafaxine in headache prevention.

CT Check Tags: Female; Male
 Adolescent
 Adult
 Aged
 Ambulatory Care Facilities
 Anxiety: CO, complications
 Chronic Disease
 Cyclohexanols: AD, administration & dosage
 *Cyclohexanols: TU, therapeutic use
 Delayed-Action Preparations
 Depression: CO, complications
 Humans
 Middle Aged
 Migraine: CL, classification
 Migraine: CO, complications
 *Migraine: PC, prevention & control
 Pain Measurement
 Research Support, Non-U.S. Gov't
 Retrospective Studies
 Serotonin Uptake Inhibitors: AD, administration & dosage
 *Serotonin Uptake Inhibitors: TU, therapeutic use
 Tension Headache: CL, classification
 Tension Headache: CO, complications
 *Tension Headache: PC, prevention & control
 Treatment Outcome
 RN 93413-69-5 (venlafaxine)
 CN 0 (Cyclohexanols); 0 (Delayed-Action Preparations); 0 (Serotonin Uptake Inhibitors)

L91 ANSWER 75 OF 313 MEDLINE on STN
 ACCESSION NUMBER: 2001472974 MEDLINE
 DOCUMENT NUMBER: PubMed ID: 11098421
 TITLE: Use of venlafaxine in other psychiatric disorders.
 AUTHOR: Ninan P T
 CORPORATE SOURCE: Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, Georgia 30322, USA.. philninan@learnlink.emory.edu
 SOURCE: Depression and anxiety, (2000) 12 Suppl 1 90-4. Ref: 29
 Journal code: 9708816. ISSN: 1091-4269.
 PUB. COUNTRY: United States
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
 General Review; (REVIEW)
 (REVIEW, TUTORIAL)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 200108
 ENTRY DATE: Entered STN: 20010827
 Last Updated on STN: 20010827
 Entered Medline: 20010823

AB Venlafaxine is a medication available by prescription in the U.S. both in an immediate release and an extended release formulation. Preclinical studies indicate it has the effect of potently blocking the **serotonin** and **norepinephrine** transporters. Venlafaxine is approved by the FDA for the treatment of major depressive

disorder and generalized anxiety disorder. Suggestive evidence, mostly from open label case series, indicates efficacy of venlafaxine in several other conditions including panic disorder, social anxiety disorder, obsessive compulsive disorder, trichotillomania, ADHD, chronic **pain**, and fibromyalgia. The limited evidence supporting efficacy in these conditions is reviewed. Additional randomized clinical trials with placebo controls are indicated.

CT *Anxiety: DT, drug therapy
 *Attention Deficit Disorder with Hyperactivity: DT, drug therapy
 Clinical Trials
 *Cyclohexanols: TU, therapeutic use
 ***Depressive Disorder, Major: DT, drug therapy**
 *Fibromyalgia: DT, drug therapy
 Humans
 *Obsessive-Compulsive Disorder: DT, drug therapy
 *Panic Disorder: DT, drug therapy
 *Phobic Disorders: DT, drug therapy
 ***Serotonin Uptake Inhibitors: TU, therapeutic use**
 *Trichotillomania: DT, drug therapy
 RN 93413-69-5 (venlafaxine)
 CN 0 (Cyclohexanols); 0 (Serotonin **Uptake Inhibitors**)

L91 ANSWER 76 OF 313 MEDLINE on STN
 ACCESSION NUMBER: 2001337451 MEDLINE
 DOCUMENT NUMBER: PubMed ID: 11319571
 TITLE: The management challenges of chronic **pain**: the role of **antidepressants**.
 AUTHOR: Barkin R L; Fawcett J
 CORPORATE SOURCE: Departments of Anesthesiology, Family Practice, and Pharmacology, The Rush Pain Center, Chicago, IL 60612, USA.
 SOURCE: American journal of therapeutics, (2000 Jan) 7 (1) 31-47.
 Ref: 105
 Journal code: 9441347. ISSN: 1075-2765.
 PUB. COUNTRY: United States
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
 General Review; (REVIEW)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 200106
 ENTRY DATE: Entered STN: 20010618
 Last Updated on STN: 20010618
 Entered Medline: 20010614

AB Chronic **pain** is both difficult for patients to tolerate and for clinicians to treat effectively. It differs from other types of **pain** in etiology and impact, which in turn affects the duration and modalities of treatment options. Forty years of research have confirmed the efficacy of **antidepressant** agents in the management of chronic **pain**, yet these agents are used inadequately. A significant amount of evidence supports the use of the traditional tricyclic **antidepressants** (TCAs) in the management of chronic **pain**, but because of their acute synaptic effects on multiple, nontherapeutic receptor systems, they are associated with numerous undesirable side effects. The newer selective serotonin **reuptake inhibitors** (SSRIs) have, comparatively, only serotonin-receptor-mediated side effects. These agents have not been thoroughly studied in the treatment of chronic **pain**. Moreover, because SSRIs impact reuptake of only one monoamine system, it is plausible that they may be less efficacious than the TCAs in treating chronic **pain**. Venlafaxine, the first agent in the new class of

serotonin (5-HT)-norepinephrine (NE) reuptake inhibitors, is unique because it **inhibits reuptake** of both 5-HT and NE (and to a lesser extent dopamine), as do some of the TCAs; however, it accomplishes this without affecting other nontherapeutic receptors. Venlafaxine is at least as effective as the TCAs, but is more tolerable, because it lacks the receptor-mediated side effects common to the TCAs. The unique characteristics of venlafaxine, including minimal cytochrome P-450 drug interaction, may make it a particularly useful **antidepressant** in the adjunctive treatment of chronic pain.

CT ***Antidepressive Agents: TU, therapeutic use**

Chronic Disease

Disease Management

Humans

Pain: DT, drug therapy

***Pain: PP, physiopathology**

CN 0 (**Antidepressive Agents**)

L91 ANSWER 77 OF 313 MEDLINE on STN

ACCESSION NUMBER: 1999420259 MEDLINE

DOCUMENT NUMBER: PubMed ID: 10492510

TITLE: Raynaud's syndrome in a patient treated with milnacipran.

AUTHOR: Bourgade B; Jonville-Bera A P; Le Gare C; Ferquel D; Autret-Leca E

SOURCE: Annals of pharmacotherapy, (1999 Sep) 33 (9) 1009-10.
Journal code: 9203131. ISSN: 1060-0280.

PUB. COUNTRY: United States

DOCUMENT TYPE: (CASE REPORTS)

Letter

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199910

ENTRY DATE: Entered STN: 19991026

Last Updated on STN: 19991026

Entered Medline: 19991012

CT Check Tags: Female

Adult

***Antidepressive Agents: AE, adverse effects**

Antidepressive Agents: TU, therapeutic use

***Cyclopropanes: AE, adverse effects**

Cyclopropanes: TU, therapeutic use

Depression: DT, drug therapy

Humans

***Raynaud Disease: CI, chemically induced**

Raynaud Disease: PA, pathology

***Serotonin Uptake Inhibitors: AE, adverse effects**

Serotonin Uptake Inhibitors: TU, therapeutic use

RN **92623-85-3 (milnacipran)**

CN 0 (**Antidepressive Agents**); 0 (**Cyclopropanes**); 0 (**Serotonin Uptake Inhibitors**)

L91 ANSWER 78 OF 313 MEDLINE on STN

ACCESSION NUMBER: 1999420258 MEDLINE

DOCUMENT NUMBER: PubMed ID: 10492509

TITLE: Diaphoresis and pruritus with extended-release venlafaxine.

AUTHOR: Schwartz T L

SOURCE: Annals of pharmacotherapy, (1999 Sep) 33 (9) 1009.

Journal code: 9203131. ISSN: 1060-0280.

PUB. COUNTRY: United States

DOCUMENT TYPE: (CASE REPORTS)
Letter
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199910
ENTRY DATE: Entered STN: 19991026
Last Updated on STN: 19991026
Entered Medline: 19991012

CT Check Tags: Female
Aged

*Antidepressive Agents, Second-Generation: AE, adverse effects
Antidepressive Agents, Second-Generation: TU, therapeutic use
*Cyclohexanols: AE, adverse effects
Cyclohexanols: TU, therapeutic use
Delayed-Action Preparations
Depression: DT, drug therapy
Humans
*Pruritus: CI, chemically induced
*Sweating: DE, drug effects

RN 93413-69-5 (venlafaxine)

CN 0 (Antidepressive Agents, Second-Generation); 0 (Cyclohexanols); 0
(Delayed-Action Preparations)

L91 ANSWER 79 OF 313 MEDLINE on STN

ACCESSION NUMBER: 1999167649 MEDLINE

DOCUMENT NUMBER: PubMed ID: 10066874

TITLE: Therapy of early poststroke depression with venlafaxine:
safety, tolerability, and efficacy as determined in an
open, uncontrolled clinical trial.

AUTHOR: Dahmen N; Marx J; Hopf H C; Tettenborn B; Roder R

SOURCE: Stroke; a journal of cerebral circulation, (1999 Mar) 30
(3) 691-2.

Journal code: 0235266. ISSN: 0039-2499.

PUB. COUNTRY: United States

DOCUMENT TYPE: (CLINICAL TRIAL)

Letter

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199904

ENTRY DATE: Entered STN: 19990426

Last Updated on STN: 19990426

Entered Medline: 19990413

CT Check Tags: Female; Male
Aged

*Antidepressive Agents, Second-Generation: TU, therapeutic use
*Cerebrovascular Disorders: CO, complications
*Cyclohexanols: TU, therapeutic use
*Depression: DT, drug therapy
Depression: ET, etiology
Humans

RN 93413-69-5 (venlafaxine)

CN 0 (Antidepressive Agents, Second-Generation); 0 (Cyclohexanols)

L91 ANSWER 80 OF 313 MEDLINE on STN

ACCESSION NUMBER: 1999277545 MEDLINE

DOCUMENT NUMBER: PubMed ID: 10350042

TITLE: Venlafaxine in the treatment of resistant postpsychotic
depressive symptoms of schizophrenia.

AUTHOR: Mazeh D; Melamed Y; Elizur A

SOURCE: Journal of clinical psychopharmacology, (1999 Jun) 19 (3)
284-5.
Journal code: 8109496. ISSN: 0271-0749.
PUB. COUNTRY: United States
DOCUMENT TYPE: (CASE REPORTS)
Letter
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199907
ENTRY DATE: Entered STN: 19990806
Last Updated on STN: 19990806
Entered Medline: 19990727

CT Check Tags: Male

*Antidepressive Agents, Second-Generation: TU, therapeutic use
*Cyclohexanols: TU, therapeutic use
*Depression: DT, drug therapy
Depression: ET, etiology
Drug Resistance
Humans
Middle Aged
Schizophrenia: CO, complications
Schizophrenia: DT, drug therapy

RN 93413-69-5 (venlafaxine)

CN 0 (Antidepressive Agents, Second-Generation); 0 (Cyclohexanols)

L91 ANSWER 81 OF 313 MEDLINE on STN

ACCESSION NUMBER: 2000037168 MEDLINE

DOCUMENT NUMBER: PubMed ID: 10570590

TITLE: Antidepressant-induced bruxism successfully treated with
gabapentin.

AUTHOR: Brown E S; Hong S C

CORPORATE SOURCE: Department of Psychiatry, University of Texas Southwestern
Medical Center, Dallas 75235-9101, USA.

SOURCE: Journal of the American Dental Association, (1999 Oct) 130
(10) 1467-9.

Journal code: 7503060. ISSN: 0002-8177.

PUB. COUNTRY: United States

DOCUMENT TYPE: (CASE REPORTS)
Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Dental Journals; Priority Journals

ENTRY MONTH: 199911

ENTRY DATE: Entered STN: 20000111
Last Updated on STN: 20000111
Entered Medline: 19991123

AB BACKGROUND: Symptoms consistent with bruxism are a common chief complaint
in dental practice. The authors describe a case of bruxism likely induced
by the antidepressant venlafaxine and successfully treated with
gabapentin. CASE DESCRIPTION: A case of bruxism, anxiety, insomnia and
tremor is reported in a man with bipolar disorder that developed a few
days after he initiated venlafaxine therapy for depression. The patient's
psychiatrist prescribed gabapentin for anxiety symptoms, and shortly
thereafter the man experienced a complete resolution of the bruxism.
CLINICAL IMPLICATIONS: On the basis of this case and the available
literature, the authors conclude that bruxism secondary to antidepressant
therapy may be common. Thus, dentists should inquire about the use of
these medications in patients who have bruxism. Gabapentin may offer
promise in the treatment of this condition.

CT Check Tags: Male

*Acetic Acids: TU, therapeutic use
 *Amines
 *Anti-Anxiety Agents: TU, therapeutic use
 *Antidepressive Agents, Second-Generation: AE, adverse effects
 Antidepressive Agents, Second-Generation: TU, therapeutic use
 *Bipolar Disorder: DT, drug therapy
 *Bruxism: CI, chemically induced
 *Bruxism: DT, drug therapy
 *Cyclohexanecarboxylic Acids
 *Cyclohexanols: AE, adverse effects
 Cyclohexanols: TU, therapeutic use
 Depression: DT, drug therapy

Humans

Middle Aged

Research Support, Non-U.S. Gov't

*gamma-Aminobutyric Acid

RN 56-12-2 (gamma-Aminobutyric Acid); 60142-96-3 (gabapentin);
 93413-69-5 (venlafaxine)

CN 0 (Acetic Acids); 0 (Amines); 0 (Anti-Anxiety Agents); 0 (Antidepressive Agents, Second-Generation); 0 (Cyclohexanecarboxylic Acids); 0 (Cyclohexanols)

L91 ANSWER 82 OF 313 MEDLINE on STN

ACCESSION NUMBER: 2000066249 MEDLINE

DOCUMENT NUMBER: PubMed ID: 10598302

TITLE: [Clinico-economic assessment of milnacipran in the prevention of depressive episodes].
 Evaluation medico-economique de milnacipran dans la prevention des episodes depressifs.

AUTHOR: Lafuma A; Dardennes R; Fagnani F; Pribil C; Bisserte J C; Berdeaux G

CORPORATE SOURCE: CEMKA, Bourg-la-Reine.

SOURCE: L'Encephale, (1999 Sep-Oct) 25 (5) 401-7.
 Journal code: 7505643. ISSN: 0013-7006.

PUB. COUNTRY: France

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: French

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200002

ENTRY DATE: Entered STN: 20000209

Last Updated on STN: 20000209

Entered Medline: 20000201

AB The objective of this study was to evaluate, for patients at risk of a new depressive episode, the net cost of maintenance therapy with milnacipran compared with a symptomatic treatment of further episodes. Using clinical decision analysis techniques, a Markov-state transition was constructed to estimate the 12 months direct costs of the two therapeutic strategies. Model construction and probabilities for performing the analysis were primarily based on a controlled phase III clinical trial demonstrating the prophylactic efficacy of milnacipran compared to placebo. Others parameters and unit costs were obtained from published sources. For each group (maintenance and episodic treatment groups), the model simulated the clinical evolution of patients on 6 successive 2-months cycles. Costs were affected for each health state period (remission, depression, abandonment of health care, suicide). The baseline analysis showed the mean costs per patient and year were 627 FF (105 US\$) higher for maintenance treatment. Sensitivity analysis suggested that costs were equal under a 25% rate of hospitalization hypothesis for a depressive episode. Maintenance costs were 1,587 FF (265 US\$) lower than episodic

treatment costs for depressed subjects with a good initial response to milnacipran (HDRS-21 score at remission < 5); this economic benefit remained under a lower rate of hospitalization hypothesis (12%). Based on the study assumptions, maintenance treatment with milnacipran appears to be clinically and economically justified for patients at high risk of hospitalization when having a recurrence, and even more for patients with an excellent initial acute response.

CT Check Tags: Comparative Study; Female; Male
Acute Disease
Adult

Antidepressive Agents: EC, economics

***Antidepressive Agents: TU, therapeutic use**

Clinical Trials

Cost-Benefit Analysis

Cyclopropanes: EC, economics

***Cyclopropanes: TU, therapeutic use**

***Depression: EC, economics**

***Depression: PC, prevention & control**

English Abstract

Follow-Up Studies

France

Humans

Markov Chains

***Mental Health Services: EC, economics**

Recurrence: PC, prevention & control

Treatment Outcome

RN 92623-85-3 (milnacipran)

CN 0 (Antidepressive Agents); 0 (Cyclopropanes)

L91 ANSWER 83 OF 313 MEDLINE on STN

ACCESSION NUMBER: 2000006156 MEDLINE

DOCUMENT NUMBER: PubMed ID: 10534584

TITLE: Effects of noradrenergic and serotonergic
antidepressants on chronic low back pain
intensity.

COMMENT: Comment in: Pain. 2000 Nov;88(2):217; author reply 218.
PubMed ID: 11203464

AUTHOR: Atkinson J H; Slater M A; Wahlgren D R; Williams R A;
Zisook S; Pruitt S D; Epping-Jordan J E; Patterson T L;
Grant I; Abramson I; Garfin S R

CORPORATE SOURCE: Department of Psychiatry, School of Medicine, University of
California San Diego, 9500 Gilman Drive, La Jolla, CA
92093-0603, USA.. jhatkinson@ucsd.edu

CONTRACT NUMBER: MO1-RR00827 (NCRR)

SOURCE: Pain, (1999 Nov) 83 (2) 137-45.

Journal code: 7508686. ISSN: 0304-3959.

PUB. COUNTRY: Netherlands

DOCUMENT TYPE: (CLINICAL TRIAL)

Journal; Article; (JOURNAL ARTICLE)

(MULTICENTER STUDY)

(RANDOMIZED CONTROLLED TRIAL)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199912

ENTRY DATE: Entered STN: 20000113

Last Updated on STN: 20010813

Entered Medline: 19991217

AB To understand the relative efficacy of noradrenergic and serotonergic
antidepressants as analgesics in chronic back pain

without **depression**, we conducted a randomized, double-blind, placebo-control head-to-head comparison of maprotiline (a **norepinephrine** reuptake blocker) and paroxetine (a **serotonin** reuptake blocker) in 103 patients with chronic low back **pain**. Of these 74 completed the trial; of the 29 who did not complete, 19 were withdrawn because of adverse effects. The intervention consisted of an 8-week course of maprotiline (up to 150 mg daily) or paroxetine (up to 30 mg daily) or an active placebo, diphenhydramine hydrochloride (up to 37.5 mg daily). Patients were excluded for current major **depression**. Reduction in **pain** intensity (Descriptor Differential Scale scores) was significantly greater for study completers randomized to maprotiline compared to placebo ($P=0.023$), and to paroxetine ($P=0.013$), with a reduction of **pain** by 45% compared to 27% on placebo and 26% on paroxetine. These results suggest that at standard dosages noradrenergic agents may provide more effective analgesia in back **pain** than do selective serotonergic **reuptake inhibitors**.

CT Check Tags: Comparative Study

Adrenergic Uptake Inhibitors: AE, adverse effects

***Adrenergic Uptake Inhibitors: TU, therapeutic use**

Adult

Aged

Chronic Disease

Diphenhydramine: AE, adverse effects

Diphenhydramine: TU, therapeutic use

Double-Blind Method

Humans

Hypnotics and Sedatives: AE, adverse effects

Hypnotics and Sedatives: TU, therapeutic use

***Low Back Pain: DT, drug therapy**

***Low Back Pain: PP, physiopathology**

Maprotiline: AE, adverse effects

*Maprotiline: TU, therapeutic use

Middle Aged

Pain Measurement

Paroxetine: AE, adverse effects

*Paroxetine: TU, therapeutic use

Patient Selection

Placebos

Research Support, U.S. Gov't, Non-P.H.S.

Research Support, U.S. Gov't, P.H.S.

Serotonin Uptake Inhibitors: AE, adverse effects

***Serotonin Uptake Inhibitors: TU, therapeutic use**

RN 10262-69-8 (Maprotiline); 58-73-1 (Diphenhydramine); 61869-08-7 (Paroxetine)

CN 0 (Adrenergic **Uptake Inhibitors**); 0 (Hypnotics and Sedatives); 0 (Placebos); 0 (Serotonin **Uptake Inhibitors**)

L91 ANSWER 84 OF 313 MEDLINE on STN

ACCESSION NUMBER: 1999184285 MEDLINE

DOCUMENT NUMBER: PubMed ID: 10086481

TITLE: SSRIs and SMRIs: broad spectrum of efficacy beyond major **depression**.

AUTHOR: Gorman J M; Kent J M

CORPORATE SOURCE: Department of Clinical Psychobiology, New York State Psychiatric Institute, College of Physicians and Surgeons of Columbia University, New York 10032, USA.

CONTRACT NUMBER: MH-00416 (NIMH)

SOURCE: Journal of clinical psychiatry, (1999) 60 Suppl 4 33-8;
discussion 39. Ref: 35
Journal code: 7801243. ISSN: 0160-6689.

PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)

LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199903
ENTRY DATE: Entered STN: 19990402
Last Updated on STN: 19990402
Entered Medline: 19990325

AB Originally studied and introduced for the treatment of **depression**, the selective **serotonin reuptake inhibitors** (SSRIs) and **serotonin/norepinephrine reuptake inhibitors** (SNRIs) have proven effective for a broad range of psychiatric illnesses, including several anxiety disorders, bulimia, and dysthymia. These drugs have in common important effects on the serotonergic (5-HT) neurotransmission system, which is involved in mediating a substantial number of important functions, including mood, aggression, sexual behavior, and **pain**. In addition, some of the new **antidepressants**, like venlafaxine/venlafaxine XR, also have effects on the noradrenergic neurotransmission system, which also appears important in mood and anxiety disorders. These new drugs, because of their specificity for the **serotonin** and **norepinephrine** reuptake proteins, lack most of the adverse side effects of tricyclic **antidepressants** and monoamine oxidase inhibitors. Consequently, in addition to being the usual first-line treatments for major **depression**, they are also first-line for panic disorder, obsessive-compulsive disorder, social phobia, posttraumatic stress disorder, and bulimia. They may also be the best medication treatments for dysthymia and generalized anxiety disorder. Further advances in psychopharmacology will be driven by discoveries from brain imaging and molecular biological research.

CT **Adrenergic Uptake Inhibitors: PD, pharmacology**
***Adrenergic Uptake Inhibitors: TU, therapeutic use**
Antidepressive Agents, Tricyclic: TU, therapeutic use
Anxiety Disorders: DT, drug therapy
Bulimia: DT, drug therapy
***Depressive Disorder: DT, drug therapy**
Dysthymic Disorder: DT, drug therapy
Humans
*Mental Disorders: DT, drug therapy
Norepinephrine: AI, antagonists & inhibitors
Norepinephrine: PK, pharmacokinetics
Obsessive-Compulsive Disorder: DT, drug therapy
Panic Disorder: DT, drug therapy
Research Support, U.S. Gov't, P.H.S.
***Serotonin Uptake Inhibitors: TU, therapeutic use**
Stress Disorders, Post-Traumatic: DT, drug therapy

RN 51-41-2 (Norepinephrine)

CN 0 (Adrenergic Uptake Inhibitors); 0 (
Antidepressive Agents, Tricyclic); 0 (**Serotonin Uptake Inhibitors**)

L91 ANSWER 85 OF 313 MEDLINE on STN
ACCESSION NUMBER: 1998225392 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9564231

TITLE: [Pharma-Clinics. The drug of the month. Venlafaxine (Efexor)].
Pharma-Clinics. Le medicament du mois. La venlafaxine (Efexor).

AUTHOR: Ansseau M

CORPORATE SOURCE: Universite de Liege, Service de Psychiatrie et de Psychologie medicale.

SOURCE: Revue medicale de Liege, (1998 Feb) 53 (2) 106-8.
Journal code: 0404317. ISSN: 0370-629X.

PUB. COUNTRY: Belgium

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: French

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199805

ENTRY DATE: Entered STN: 19980609
Last Updated on STN: 19980609
Entered Medline: 19980528

AB Venlafaxine (Efexor) is the first representative of a new class of antidepressants: serotonin noradrenaline reuptake inhibitors. Its usual dose is 75 mg/d in two intakes but can be progressively increased until a maximal daily dose of 375 mg/d in severe or resistant depression, particularly among inpatients. The efficacy of venlafaxine is at least equivalent to reference antidepressants. At high doses, venlafaxine could even exhibit a better efficacy and a shorter latency than current compounds. Its profile of side-effects is quite similar to selective serotonin reuptake inhibitors with mainly nausea, with the exception if an increase in blood pressure which can appear at high doses. In total, venlafaxine represents an interesting innovation in the pharmacological treatment of depression.

CT **Antidepressive Agents, Second-Generation: AD, administration & dosage**
Antidepressive Agents, Second-Generation: AE, adverse effects
Antidepressive Agents, Second-Generation: PK, pharmacokinetics
***Antidepressive Agents, Second-Generation: TU, therapeutic use**
 Blood Pressure: DE, drug effects
 Cyclohexanols: AD, administration & dosage
 Cyclohexanols: AE, adverse effects
 Cyclohexanols: PK, pharmacokinetics
 *Cyclohexanols: TU, therapeutic use
Depression: DT, drug therapy
 Drug Administration Schedule
 English Abstract
 Humans
 Hypertension: CI, chemically induced
 Nausea: CI, chemically induced
 Serotonin Uptake Inhibitors: AD, administration & dosage
 Serotonin Uptake Inhibitors: AE, adverse effects
 Serotonin Uptake Inhibitors: PK, pharmacokinetics
 *Serotonin Uptake Inhibitors: TU, therapeutic use
 Therapeutic Equivalency

RN **93413-69-5 (venlafaxine)**

CN 0 (Antidepressive Agents, Second-Generation); 0 (Cyclohexanols); 0 (Serotonin Uptake Inhibitors)

L91 ANSWER 86 OF 313 MEDLINE on STN

ACCESSION NUMBER: 1998365702 MEDLINE

DOCUMENT NUMBER: PubMed ID: 9700345

TITLE: Venlafaxine withdrawal reactions.

AUTHOR: Boyd I W

CORPORATE SOURCE: Adverse Drug Reactions Advisory Committee, Woden, ACT.
SOURCE: Medical journal of Australia, (1998 Jul 20) 169 (2) 91-2.
Journal code: 0400714. ISSN: 0025-729X.
PUB. COUNTRY: Australia
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199808
ENTRY DATE: Entered STN: 19980828
Last Updated on STN: 19980828
Entered Medline: 19980818

CT Check Tags: Female; Male
Adult

***Antidepressive Agents, Second-Generation: AE, adverse effects**

*Anxiety: CI, chemically induced

*Cyclohexanols: AE, adverse effects

Depression: DT, drug therapy

Depressive Disorder: DT, drug therapy

Dizziness: CI, chemically induced

Fatigue: CI, chemically induced

Hallucinations: CI, chemically induced

*Headache: CI, chemically induced

Humans

Middle Aged

*Nausea: CI, chemically induced

*Sensation Disorders: CI, chemically induced

*Substance Withdrawal Syndrome: ET, etiology

Tinnitus: CI, chemically induced

RN 93413-69-5 (venlafaxine)

CN 0 (Antidepressive Agents, Second-Generation); 0 (Cyclohexanols)

L91 ANSWER 87 OF 313 MEDLINE on STN

ACCESSION NUMBER: 1998136297 MEDLINE

DOCUMENT NUMBER: PubMed ID: 9475820

TITLE: Hyponatremia with venlafaxine.

COMMENT: Comment in: Ann Pharmacother. 1998 Sep;32(9):981-2. PubMed
ID: 9762390

AUTHOR: Masood G R; Karki S D; Patterson W R

CORPORATE SOURCE: Long Term Care Division, Clifton Springs Hospital and
Clinic, NY, USA.

SOURCE: Annals of pharmacotherapy, (1998 Jan) 32 (1) 49-51.

Journal code: 9203131. ISSN: 1060-0280.

PUB. COUNTRY: United States

DOCUMENT TYPE: (CASE REPORTS)

Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199803

ENTRY DATE: Entered STN: 19980319

Last Updated on STN: 20000303

Entered Medline: 19980311

AB OBJECTIVE: To describe a patient with hyponatremia associated with
venlafaxine therapy. CASE SUMMARY: A 92-year old white woman who was
receiving venlafaxine for management of depression was found to have
hyponatremia. A detailed workup confirmed the diagnosis of syndrome of
inappropriate antidiuretic hormone secretion (SIADH). A temporal
relationship between initiation of venlafaxine therapy and the onset of
hyponatremia indicated it as the probable cause. Venlafaxine was
discontinued, and hyponatremia resolved with a few weeks. DISCUSSION:

Hyponatremia has been reported with selective serotonin-reuptake inhibitors (SSRIs). Serotonin has been reported to elevate concentrations of vasopressin in animal models. Venlafaxine is a potent inhibitor of serotonin reuptake and may have adverse effects similar to those of SSRIs. CONCLUSIONS: We report a case of hyponatremia probably caused by venlafaxine. Awareness of this potential problem would be helpful to clinicians and should be considered in the differential diagnosis of hyponatremia.

CT Check Tags: Female

Aged

Aged, 80 and over

*Antidepressive Agents, Second-Generation: AE, adverse effects

Antidepressive Agents, Second-Generation: TU, therapeutic use

*Cyclohexanols: AE, adverse effects

Cyclohexanols: TU, therapeutic use

Depression: DT, drug therapy

Humans

*Hyponatremia: CI, chemically induced

*Serotonin Uptake Inhibitors: AE, adverse effects

Serotonin Uptake Inhibitors: TU, therapeutic use

RN 93413-69-5 (venlafaxine)

CN 0 (Antidepressive Agents, Second-Generation); 0 (Cyclohexanols); 0 (Serotonin Uptake Inhibitors)

L91 ANSWER 88 OF 313 MEDLINE on STN

ACCESSION NUMBER: 2005174280 MEDLINE

DOCUMENT NUMBER: PubMed ID: 12799988

TITLE: [The opioid tramadol demonstrates excitatory properties of non-opioid character--a preclinical study using alfentanil as a comparison].

Das Opioid Tramadol hat zentral-exzitatorische Effekte von nicht-opioidartigem Charakter. Teil 1: Praktinische Ergebnisse im Vergleich zu Alfentanil.

AUTHOR: Freye E; Latasch L; Von Bredow G; Neruda B

CORPORATE SOURCE: Abteilung fur Gefasschirurgie und Nierentransplantation, Operatives Zentrum, Heinrich-Heine-Universitat Dusseldorf.

SOURCE: Schmerz (Berlin, Germany), (1998 Feb 28) 12 (1) 19-24.

Journal code: 8906258. ISSN: 0932-433X.

PUB. COUNTRY: Germany: Germany, Federal Republic of

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: German

FILE SEGMENT: NONMEDLINE; PUBMED-NOT-MEDLINE

ENTRY MONTH: 200504

ENTRY DATE: Entered STN: 20050406

Last Updated on STN: 20050406

Entered Medline: 20050405

AB Tramadol, an analgesic with mean potency one tenth that of morphine is used regularly for the treatment of chronic and postoperative **pain**. Previous reports have indicated that tramadol may induce seizure activity when given together with a selective serotonin **reuptake inhibitor** (SSRI). Therefore, its major mode of action may be questioned which purportedly is due to binding with the opioid receptor and partly due to the **inhibition** of monoamine **reuptake**. We therefore set out to study its potential in inducing seizure activity and to quantify its effect on EEG-power spectra and on the central modulation of sensory afferents in awake and trained dogs (n=7). In order to demonstrate if opioid receptors mediated these effects, incremental doses of tramadol were given which was followed by naloxone for possible reversal. After a wash-out period the same animals were exposed to graded

doses of alfentanil, a pure mu-receptor agonist. Again this was followed by the opioid antagonist naloxone for reversal. The electroencephalogram (EEG) and the event-related evoked potentials (SEP) were used to demonstrate possible excitatory effects. In order to derive the SEP the front paw was stimulated electrically (Digi Stim II trade mark) while the evoked potentials were picked up contralaterally from the somatosensory cortex using stick-on electrodes. 256 sweeps were averaged (Lifescan) and the peak-to-peak amplitude was measured to demonstrate CNS excitation compared to control (%). Additionally, the raw electroencephalogram was viewed for epileptogenic changes and its power computed into the various power bands alpha, beta, delta and theta using FFT over a time epoch of 60 s. Following control, graded doses of either tramadol (2-5-10 mg/kg i.v.) or alfentanil (10-30-60 microg/kg i.v.) were given every 15 min while the EEG and the SEP were recorded. Thereafter naloxone (20 microg/kg i.v.) was injected for reversal. Tramadol did not suppress the amplitude of the SEP at any dose. High doses (>5 mg/kg i.v.) resulted in an increase (+100%) of the amplitude of the evoked potential. This was accompanied by short-term muscle fibrillations, and a short-term spike-and-wave activity in the EEG followed by a long-lasting theta-dominance. These effects could not be reversed by naloxone. In contrast to tramadol, alfentanil induced a dose-related **depression** of amplitude in the SEP with a maximum of 82% suggesting a **depressive** effect of modulation of afferents in the sensory cortex. This effect was fully naloxone reversible and was followed by a rebound in amplitude of the SEP together with an increase in fast beta-waves in the EEG. Tramadol very little mediates its central action via the mu-opioid receptor as the present effects were not naloxone reversible. Consistent with the results is the very low affinity of tramadol to the opioid receptor which is several thousand times less than that of morphine. Most likely, inhibition of central **norepinephrine** and **serotonin** reuptake as well as the reduction in 5-HT-turnover may contribute to the effects of tramadol. Due to the monoamine **reuptake inhibition** an increase in transmission may result, triggering off excitatory phenomena with spike-and-wave activity in the CNS. Such excitatory effects, however, may only be seen when tramadol is used in doses exceeding the therapeutic range.

CT English Abstract

L91 ANSWER 89 OF 313 MEDLINE on STN
ACCESSION NUMBER: 97309218 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9166385
TITLE: Treatment-resistant affective disorders.
COMMENT: Comment on: Br J Hosp Med. 1995 Nov 15-Dec 12;54(10):501-6.
PubMed ID: 8574492
AUTHOR: Bowskill R J; Bridges P K
SOURCE: British journal of hospital medicine, (1997 Feb 19-Mar 4)
57 (4) 171-2.
Journal code: 0171545. ISSN: 0007-1064.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Commentary
Letter
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199706
ENTRY DATE: Entered STN: 19970630
Last Updated on STN: 20000303
Entered Medline: 19970616

CT *Antidepressive Agents: TU, therapeutic use
*Benzamides: TU, therapeutic use

*Cyclohexanols: TU, therapeutic use

Depression: DT, drug therapy

Humans

Moclobemide

*Mood Disorders: DT, drug therapy

Therapeutic Equivalency

RN 71320-77-9 (Moclobemide); 93413-69-5 (venlafaxine)

CN 0 (Antidepressive Agents); 0 (Benzamides); 0 (Cyclohexanols)

L91 ANSWER 90 OF 313 MEDLINE on STN

ACCESSION NUMBER: 97229930 MEDLINE

DOCUMENT NUMBER: PubMed ID: 9075493

TITLE: Tramadol: a new centrally acting analgesic.

AUTHOR: Lewis K S; Han N H

CORPORATE SOURCE: Department of Pharmacy Practice, Chicago College of
Pharmacy, Midwestern University, Downers Grove, IL 60515,
USA.. klewis@rush.edu

SOURCE: American journal of health-system pharmacy : AJHP :
official journal of the American Society of Health-System
Pharmacists, (1997 Mar 15) 54 (6) 643-52. Ref: 68
Journal code: 9503023. ISSN: 1079-2082.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199711

ENTRY DATE: Entered STN: 19971224

Last Updated on STN: 19971224

Entered Medline: 19971119

AB The pharmacology, pharmacokinetics, efficacy, adverse effects, and dosage and administration of tramadol are reviewed. Tramadol is a synthetic analogue of codeine that binds to mu opiate receptors and **inhibits norepinephrine and serotonin reuptake**. It is rapidly and extensively absorbed after oral doses and is metabolized in the liver. Analgesia begins within one hour and starts to peak in two hours. In patients with moderate postoperative **pain**, i.v. or i.m. tramadol is roughly equal in efficacy to meperidine or morphine; for severe acute **pain**, tramadol is less effective than morphine. Oral tramadol can also be effective after certain types of surgery. Tramadol and meperidine are equally effective in postoperative patient-controlled analgesia. In epidural administration for **pain** after abdominal surgery, tramadol is more effective than bupivacaine but less effective than morphine. In patients with ureteral calculi, both dipyrone and butylscopolamine are more effective than tramadol. For labor **pain**, i.m. tramadol works as well as meperidine and is less likely to cause neonatal respiratory **depression**. Oral tramadol is as effective as codeine for acute dental **pain**. In several types of severe or refractory cancer **pain**, tramadol is effective, but less so than morphine; for other types of chronic **pain**, such as low-back **pain**, oral tramadol works as well as acetaminophen-codeine. Common adverse effects of tramadol include dizziness, nausea, dry mouth, and sedation. The abuse potential seems low. The recommended oral dosage is 50-100 mg every four to six hours. Tramadol is an effective, if expensive, alternative to other analgesics in some clinical situations.

CT Check Tags: Comparative Study; Female

Analgesics, Opioid: AE, adverse effects

Analgesics, Opioid: PK, pharmacokinetics
 *Analgesics, Opioid: TU, therapeutic use
 Constipation: CI, chemically induced
 Drug Interactions
 Headache: CI, chemically induced
 Humans
 Nausea: CI, chemically induced
 *Pain: DT, drug therapy
 Pregnancy
 Tramadol: AE, adverse effects
 Tramadol: PK, pharmacokinetics
 *Tramadol: TU, therapeutic use

RN 27203-92-5 (Tramadol)
 CN 0 (Analgesics, Opioid)

L91 ANSWER 91 OF 313 MEDLINE on STN
 ACCESSION NUMBER: 97386753 MEDLINE
 DOCUMENT NUMBER: PubMed ID: 9242843
 TITLE: Efficacy of venlafaxine in depressive illness in general practice.
 AUTHOR: Lecrubier Y; Bourin M; Moon C A; Schifano F; Blanchard C; Danjou P; Hackett D
 CORPORATE SOURCE: Hopital La Pitie-Salpetriere, Paris, France.
 SOURCE: Acta psychiatrica Scandinavica, (1997 Jun) 95 (6) 485-93.
 Journal code: 0370364. ISSN: 0001-690X.
 PUB. COUNTRY: Denmark
 DOCUMENT TYPE: (CLINICAL TRIAL)
 Journal; Article; (JOURNAL ARTICLE)
 (RANDOMIZED CONTROLLED TRIAL)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 199710
 ENTRY DATE: Entered STN: 19971013
 Last Updated on STN: 19971013
 Entered Medline: 19971002

AB A double-blind, placebo-controlled study of 229 patients with a Research Diagnostic Criteria diagnosis of major, minor or intermittent depression was used to compare the clinical profiles of venlafaxine and imipramine in general practice. Venlafaxine produced a significant improvement compared to placebo in symptoms of depression and anxiety as rated by the total MADRS and percentage of responders, the CGI improvement, the CGI severity of illness, the BSA psychic anxiety item and the HSCL. On a number of these measures, venlafaxine was also significantly more effective than imipramine. Venlafaxine was significantly superior to both imipramine and placebo for the SARS total score and the items 'social/leisure' and 'extended family.' A similar proportion of patients discontinued treatment in each group, but fewer patients on venlafaxine discontinued treatment because of an unsatisfactory response.

CT Check Tags: Female; Male
 Adult
 Analysis of Variance
 *Antidepressive Agents, Second-Generation: TU, therapeutic use
 Antidepressive Agents, Tricyclic: TU, therapeutic use
 Anxiety: DT, drug therapy
 *Cyclohexanols: TU, therapeutic use
 *Depression: DT, drug therapy
 Double-Blind Method
 Family Practice
 Humans

Imipramine: TU, therapeutic use
Middle Aged
Placebo Effect
Prospective Studies
Social Adjustment
Treatment Outcome

RN 50-49-7 (Imipramine); 93413-69-5 (venlafaxine)
CN 0 (Antidepressive Agents, Second-Generation); 0 (Antidepressive Agents, Tricyclic); 0 (Cyclohexanols)

L91 ANSWER 92 OF 313 MEDLINE on STN
ACCESSION NUMBER: 97274805 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9190324
TITLE: [Effectiveness and tolerance of tramadol in cancer
pain. A comparative study with respect to
buprenorphine].
Efficacite et tolerance du tramadol dans les douleurs
neoplasiques. Etude comparative par rapport a la
buprenorphine.
AUTHOR: Bono A V; Cuffari S
CORPORATE SOURCE: Service d'Urologie, Hopital di Circolo, Varese, Italie.
SOURCE: Drugs, (1997) 53 Suppl 2 40-9.
Journal code: 7600076. ISSN: 0012-6667.
PUB. COUNTRY: New Zealand
DOCUMENT TYPE: (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(RANDOMIZED CONTROLLED TRIAL)
LANGUAGE: French
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199706
ENTRY DATE: Entered STN: 19970630
Last Updated on STN: 19970630
Entered Medline: 19970619

AB Opioid analgesics represent one of the most important tools in a sequential pharmacological approach to oncological **pain** relief. They are recommended by the WHO when nonsteroidal anti-inflammatory drugs (NSAIDs) no longer provide adequate analgesia. However, the use of opioids is limited because of their numerous and often severe adverse effects. This aspect of opioids has motivated continuous research projects aimed at discovering drugs that can provide maximum **pain** relief but with improved tolerability. Tramadol is a new, centrally acting analgesic with a dual mechanism of action. It shows a selective interaction with mu receptors, which are responsible for nociception, and has weak pharmacodynamic activity on other opioid receptors. At the same time, it acts synergistically on neuroamine transmission by **inhibiting** synaptic noradrenaline (**norepinephrine**) **reuptake** and inducing intrasynaptic **serotonin** (5-hydroxytryptamine; 5-HT) release. From a pharmacokinetic standpoint, tramadol offers high bioavailability, with similar patterns after oral or parenteral administration (half-life 5 to 7 hours, time to peak plasma concentration 3.1 hours, and approximately 20% plasma protein binding). Although the efficacy of tramadol is comparable to that of other drugs with similar modes of action, the incidence of side effects such as constipation and respiratory **depression** is lower. The frequency of euphoria and dysphoria is negligible, resulting in little risk of abuse or dependence. It therefore seemed appropriate to further investigate the efficacy and tolerability of tramadol, defined as having only weak potency, in comparison with a widely used opioid, in oncological **pain**. Buprenorphine was selected as an opioid with a potency

equivalent to half that of morphine, but with tolerability that is partially limited by the fact that it frequently gives rise to adverse reactions considered typical of stronger opioids. To compare the analgesic effect and tolerability of tramadol and buprenorphine, 60 patients (44 men, 16 women; average age 61.4 years), all presenting with advanced tumours, were treated orally in a controlled crossover trial with randomised sequences. Patients took both drugs, each for a week, with a 24-hour washout period between treatments. Tramadol was prescribed at the daily dose of 300mg, orally, and buprenorphine at 0.6 mg/day, as a sublingual preparation. Assessments were made of Karnofsky performance status and severity of **pain** before and during the 4 hours after taking the 2 drugs. Each patient also completed a daily diary recording the severity of **pain** 1 hour after the dose, the evolution of **pain** during the day and its severity compared with that on the previous day. They also assessed the duration and quality of sleep. The Karnofsky index changed little with either treatment, but all other variables showed worthwhile improvement, indicating the significant analgesic effect of both drugs. Buprenorphine and tramadol had a similar analgesic effect, although the improvement with the test drug was significant within 1 hour of administration ($p < 0.05$ compared with baseline) and more marked ($p < 0.05$ on day 2 compared with buprenorphine). At the end of tramadol treatment, sleep had also improved, both quantitatively and qualitatively (both $p < 0.05$). The final assessment was significantly in favour of tramadol as regards efficacy ($p < 0.05$) and patient acceptability ($p < 0.01$). Thus, tramadol was better tolerated than buprenorphine, and caused fewer and milder adverse reactions. Only 1 patient discontinued tramadol, compared with 18 using reference therapy. Tramadol, although theoretically less potent, nevertheless brought about as much **pain** relief as the comparator opioid. In conclusion, for this class of drug, tramadol provides an excellent balance between efficacy and tolerability, confirming preliminary studies.

CT Check Tags: Comparative Study; Female; Male

Aged

Aged, 80 and over

Analgesics, Opioid: AE, adverse effects

*Analgesics, Opioid: TU, therapeutic use

Analysis of Variance

Buprenorphine: AE, adverse effects

*Buprenorphine: TU, therapeutic use

English Abstract

Humans

Middle Aged

*Neoplasms: CO, complications

*Pain: DT, drug therapy

Pain: ET, etiology

Tramadol: AE, adverse effects

*Tramadol: TU, therapeutic use

RN 27203-92-5 (Tramadol); 52485-79-7 (Buprenorphine)

CN 0 (Analgesics, Opioid)

L91 ANSWER 93 OF 313 MEDLINE on STN

ACCESSION NUMBER: 97274804 MEDLINE

DOCUMENT NUMBER: PubMed ID: 9190323

TITLE: [Treatment of post-herpes zoster **pain** with tramadol. Results of an open pilot study versus clomipramine with or without levomepromazine].
 Traitement des douleurs post-zosteriennes par le tramadol.
 Resultats d'une etude pilote ouverte versus clomipramine avec ou sans levomepromazine.

AUTHOR: Gobel H; Stadler T
CORPORATE SOURCE: Service de Neurologie, Hopital Universitaire, Kiel, Allemagne.
SOURCE: Drugs, (1997) 53 Suppl 2 34-9.
Journal code: 7600076. ISSN: 0012-6667.
PUB. COUNTRY: New Zealand
DOCUMENT TYPE: (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(RANDOMIZED CONTROLLED TRIAL)
LANGUAGE: French
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199706
ENTRY DATE: Entered STN: 19970630
Last Updated on STN: 19990129
Entered Medline: 19970619

AB To date, no universally applicable recommendations are available for the treatment of patients with postherpetic neuralgia. A mixture of clinical anecdotes, experimental findings and observations from clinical trials form the basis of the medical arsenal for this condition. Tricyclic **antidepressants** are commonly used, and clinical experience and several investigations have documented their effectiveness. Today, single entity **antidepressants**, which can be combined with neuroleptics to increase analgesia, are generally recommended for the treatment of postherpetic neuralgia. Some authors also recommend the additional administration of an opioid if analgesia is inadequate. Just over a decade ago, opioids were considered ineffective for the treatment of neuropathic **pain**; however, more recent investigations relating to the use of opioids, primarily in the treatment of nontumour-related chronic **pain**, have led to a revision of their use in neuropathic **pain**. Nevertheless, the use of opioid therapy for neurogenic **pain** remains controversial. Tramadol is a synthetic, centrally acting analgesic with both opioid and nonopioid analgesic activity. The nonopioid component is related to the **inhibition** of noradrenaline (**norepinephrine**) **reuptake** and stimulation of **serotonin** (5-hydroxytryptamine; 5-HT) release at the spinal level. In this regard, there are parallels with **antidepressants**, which are believed to potentiate the effect of biogenic amines in endogenous **pain**-relieving systems. There is evidence that, in tramadol, both mechanisms act synergistically with respect to analgesia. The aim of this pilot study was to investigate, for the first time, the analgesic efficacy and tolerability of tramadol, compared with the **antidepressant** clomipramine, in the treatment of postherpetic neuralgia. If necessary, clomipramine was used in combination with the neuroleptic levomepromazine. The study allowed individualised dosages at predetermined intervals up to a maximum daily dose of tramadol 600mg and clomipramine 100mg, or clomipramine 100mg with or without levomepromazine 100mg. 21 (60%) of 35 randomised patients (> or = 65 years) received the study medication over the 6-week period [tramadol n = 10; clomipramine with or without levomepromazine) n = 11]. After 3 weeks' treatment the dosage in both groups remained almost constant for the rest of the 6-week treatment phase (mean daily dose: tramadol 250 to 290mg; clomipramine 59.1 to 63.6mg). Only 3 patients required the combination of clomipramine and levomepromazine. At the outset, both groups recorded an average **pain** level of 'moderate' to 'very severe'. In correlation with increasing the study medication, this had decreased to 'slight' by the end of the treatment, when 9 of 10 patients in the tramadol group and of 6 of 11 patients in the clomipramine group retrospectively rated their analgesia as excellent, good or satisfactory. The psychological/physical condition of the patients did not change

significantly during tramadol treatment. Sensitivity and **depression** parameters decreased in the clomipramine group. The incidence of adverse events for all patients was similar in both groups (tramadol 76.5%; clomipramine with or without levomepromazine 83.3%). In conclusion, tramadol would appear to be an interesting therapeutic alternative for **pain** relief in postherpetic neuralgia, particularly in patients who are not **depressed**. In clinical practice, tramadol and clomipramine can best be used differentially. For example, tramadol could be the drug of first choice in patients with obvious cardiovascular disease (not an uncommon problem in the > or = 65 year age group) in whom **antidepressants** are contraindicated, and similarly in patients in whom an **antidepressant** effect is not required. (ABSTRACT TRUNCATED)

CT Check Tags: Comparative Study

Aged

Analgesics, Opioid: AE, adverse effects

*Analgesics, Opioid: TU, therapeutic use

Antidepressive Agents, Tricyclic: AE, adverse effects

***Antidepressive Agents, Tricyclic: TU, therapeutic use**

Antipsychotic Agents: AE, adverse effects

*Antipsychotic Agents: TU, therapeutic use

Clomipramine: AE, adverse effects

Clomipramine: TU, therapeutic use

Drug Therapy, Combination

English Abstract

*Herpes Zoster: CO, complications

Humans

Methotrimeprazine: AE, adverse effects

Methotrimeprazine: TU, therapeutic use

*Neuralgia: DT, drug therapy

Neuralgia: ET, etiology

Pilot Projects

Tramadol: AE, adverse effects

*Tramadol: TU, therapeutic use

RN 27203-92-5 (Tramadol); 303-49-1 (Clomipramine); 60-99-1 (Methotrimeprazine)

CN 0 (Analgesics, Opioid); 0 (**Antidepressive Agents, Tricyclic**); 0 (Antipsychotic Agents)

L91 ANSWER 94 OF 313 MEDLINE on STN

ACCESSION NUMBER: 97274802 MEDLINE

DOCUMENT NUMBER: PubMed ID: 9190321

TITLE: [Pharmacology of tramadol].
Pharmacologie du tramadol.

AUTHOR: Dayer P; Desmeules J; Collart L

CORPORATE SOURCE: Service de Pharmacologie Clinique et Consultation de la Douleur, Hopital Cantonal Universitaire, Geneve, Suisse.

SOURCE: Drugs, (1997) 53 Suppl 2 18-24. Ref: 39
Journal code: 7600076. ISSN: 0012-6667.

PUB. COUNTRY: New Zealand

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)

LANGUAGE: French

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199706

ENTRY DATE: Entered STN: 19970630

Last Updated on STN: 19970630

Entered Medline: 19970619

AB (+/-)-Tramadol is a synthetic 4-phenyl-piperidine analogue of codeine. It is a central analgesic with a low affinity for opioid receptors. Its selectivity for mu receptors has recently been demonstrated, and the M1 metabolite of tramadol, produced by liver O-demethylation, shows a higher affinity for opioid receptors than the parent drug. The rate of production of this M1 derivative (O-demethyl tramadol), is influenced by a polymorphic isoenzyme of the debrisoquine-type, cytochrome P450 2D6 (CYP2D6). Nevertheless, this affinity for mu receptors of the CNS remains low, being 6000 times lower than that of morphine. Moreover, and in contrast to other opioids, the analgesic action of tramadol is only partially inhibited by the opioid antagonist naloxone, which suggests the existence of another mechanism of action. This was demonstrated by the discovery of a monoaminergic activity that inhibits noradrenaline (**norepinephrine**) and **serotonin** (5-hydroxytryptamine; 5-HT) reuptake, making a significant contribution to the analgesic action by blocking nociceptive impulses at the spinal level. (+/-)-Tramadol is a racemic mixture of 2 enantiomers, each one displaying differing affinities for various receptors. (+/-)-Tramadol is a selective agonist of mu receptors and preferentially **inhibits serotonin reuptake** , whereas (-)-tramadol mainly **inhibits noradrenaline reuptake**. The action of these 2 enantiomers is both complementary and synergistic and results in the analgesic effect of (+/-)-tramadol. After oral administration, tramadol demonstrates 68% bioavailability, with peak serum concentrations reached within 2 hours. The elimination kinetics can be described as 2-compartmental, with a half-life of 5.1 hours for tramadol and 9 hours for the M1 derivative after a single oral dose of 100mg. This explains the approximately 2-fold accumulation of the parent drug and its M1 derivative that is observed during multiple dose treatment with tramadol. The recommended daily dose of tramadol is between 50 and 100mg every 4 to 6 hours, with a maximum dose of 400 mg/day; the duration of the analgesic effect after a single oral dose of tramadol 100mg is about 6 hours. Adverse effects, and nausea in particular, are dose-dependent and therefore considerably more likely to appear if the loading dose is high. The reduction of this dose during the first days of treatment is an important factor in improving tolerability. Other adverse effects are generally similar to those of opioids, although they are usually less severe, and can include respiratory **depression**, dysphoria and constipation. Tramadol can be administered concomitantly with other analgesics, particularly those with peripheral action, while drugs that **depress** CNS function may enhance the sedative effect of tramadol. Tramadol should not be administered to patients receiving monoamine oxidase inhibitors, and administration with tricyclic **antidepressant** drugs should also be avoided. Tramadol has pharmacodynamic and pharmacokinetic properties that are highly unlikely to lead to dependence. This was confirmed by various controlled studies and postmarketing surveillance studies, which reported an extremely small number of patients developing tolerance or instances of tramadol abuse. Tramadol is a central acting analgesic which has been shown to be effective and well tolerated, and likely to be of value for treating several **pain** conditions (step II of the World Health Organization ladder) where treatment with strong opioids is not required.

CT Administration, Oral
Administration, Rectal
Analgesics, Opioid: CH, chemistry
Analgesics, Opioid: PK, pharmacokinetics
*Analgesics, Opioid: PD, pharmacology
Animals
Codeine: CH, chemistry

Codeine: PD, pharmacology
English Abstract
Humans
Injections, Intramuscular
Injections, Intravenous
Structure-Activity Relationship
Tramadol: CH, chemistry
Tramadol: PK, pharmacokinetics
*Tramadol: PD, pharmacology

RN 27203-92-5 (Tramadol); 76-57-3 (Codeine)

CN 0 (Analgesics, Opioid)

L91 ANSWER 95 OF 313 MEDLINE on STN

ACCESSION NUMBER: 97030935 MEDLINE

DOCUMENT NUMBER: PubMed ID: 8876863

TITLE: Nefazodone: its place among **antidepressants**.

AUTHOR: Cyr M; Brown C S

CORPORATE SOURCE: College of Pharmacy, University of Tennessee, Memphis
38163, USA.

SOURCE: Annals of pharmacotherapy, (1996 Sep) 30 (9) 1006-12. Ref:
39

Journal code: 9203131. ISSN: 1060-0280.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

General Review; (REVIEW)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199701

ENTRY DATE: Entered STN: 19970128

Last Updated on STN: 19970128

Entered Medline: 19970115

AB OBJECTIVE: To review the pharmacology, pharmacokinetics, efficacy, adverse effects, and drug interactions of nefazodone as well as to determine its place among currently available **antidepressants**. DATA SOURCES: A search of European and American literature using EMBASE and MEDLINE was completed. Nefazodone was the search term. DATA SYNTHESIS: Nefazodone is an **antidepressant** that blocks serotonin type 2 (5-HT₂) receptors in addition to **inhibiting the reuptake of serotonin and norepinephrine**. In double-blind, placebo-controlled studies, nefazodone demonstrates **antidepressant** activity at dosages ranging from 400 to 600 mg/d. Sedation, dry mouth, nausea, and dizziness are the more common adverse effects of nefazodone. Nefazodone, an analog of trazodone, has not been associated with priapism at this time, and may have fewer sexual adverse effects than other **antidepressants**. More studies are needed to determine the potential role of nefazodone in treating anxiety, **pain**, and premenstrual syndrome. STUDY SELECTION: Only double-blind, placebo-controlled studies designed to establish the efficacy of nefazodone as an **antidepressant** were reviewed. CONCLUSIONS: Based on placebo-controlled, double-blind, comparative trials, nefazodone demonstrates greater efficacy than placebo, and equivalent efficacy to imipramine. Somnolence, dry mouth, nausea, dizziness, and constipation are the most common adverse effects. Nefazodone appears to have a milder adverse effect profile than the tricyclic **antidepressants**, causes fewer sexual dysfunctions than the serotonin selective **reuptake inhibitors**, and may cause less dizziness than trazodone. Nefazodone at dosages of at least 300 mg/d provides another option for the treatment of **depression**.

CT *Antidepressive Agents, Second-Generation

Antidepressive Agents, Second-Generation: AE, adverse effects
Antidepressive Agents, Second-Generation: PK, pharmacokinetics
Antidepressive Agents, Second-Generation: PD, pharmacology
Controlled Clinical Trials
Drug Interactions
Humans

***Triazoles**

Triazoles: AE, adverse effects
Triazoles: PK, pharmacokinetics
Triazoles: PD, pharmacology

RN 83366-66-9 (nefazodone)

CN 0 (**Antidepressive Agents, Second-Generation**); 0 (**Triazoles**)

L91 ANSWER 96 OF 313 MEDLINE on STN

ACCESSION NUMBER: 97124876 MEDLINE

DOCUMENT NUMBER: PubMed ID: 8969980

TITLE: Etrank: a ranking procedure for handling missing data in clinical trials: application to venlafaxine extended-release depression clinical trial.

AUTHOR: Entsuah R

CORPORATE SOURCE: Wyeth-Ayerst Research, Clinical Biostatistics, Philadelphia, Pennsylvania 19101, USA.

SOURCE: Journal of biopharmaceutical statistics, (1996 Nov) 6 (4) 457-75. Ref: 30

Journal code: 9200436. ISSN: 1054-3406.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

General Review; (REVIEW)

(REVIEW, TUTORIAL)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199703

ENTRY DATE: Entered STN: 19970407

Last Updated on STN: 19970407

Entered Medline: 19970321

AB ETRANK is a statistical software which uses nonparametric (randomization) technique to analyze incomplete repeated measures data, where the pattern of withdrawal is treatment related. This stand alone program is written in C, presently runs in MS-DOS, and a Windows version is in development. The program has been developed based on methods developed by Entsuah (1990). These methods were presented at Statistics and Statistical Graphics Section of the 1991 SAS Users Group International Conference (SUGI-16). They were also presented to the Biometric Division of US Food and Drug Administration (FDA). ETRANK is now being used by CNS group of Wyeth-Ayerst Research as part of their NDA submission. This paper discusses ETRANK, and compares it with SAS PROC MIXED, and GEE. These methods are applied to Wyeth-Ayerst antidepressant Effexor-ER (extended release) data.

CT ***Antidepressive Agents, Second-Generation: TU, therapeutic use**

***Clinical Trials: MT, methods**

***Cyclohexanols: TU, therapeutic use**

Data Interpretation, Statistical

***Depression: DT, drug therapy**

Humans

Longitudinal Studies

Mathematical Computing

***Software**

***Statistics: MT, methods**

RN 93413-69-5 (venlafaxine)

CN 0 (Antidepressive Agents, Second-Generation); 0 (Cyclohexanols)

L91 ANSWER 97 OF 313 MEDLINE on STN

ACCESSION NUMBER: 97054846 MEDLINE

DOCUMENT NUMBER: PubMed ID: 8899135

TITLE: An open-label evaluation of the long-term safety of oral venlafaxine in depressed elderly patients.

AUTHOR: Dierick M

CORPORATE SOURCE: Department of Psychiatry, University of Gent, Afsnee, Belgium.

SOURCE: Annals of clinical psychiatry : official journal of the American Academy of Clinical Psychiatrists, (1996 Sep) 8 (3) 169-78.

Journal code: 8911021. ISSN: 1040-1237.

PUB. COUNTRY: United States

DOCUMENT TYPE: (CLINICAL TRIAL)

Journal; Article; (JOURNAL ARTICLE)

(MULTICENTER STUDY)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199703

ENTRY DATE: Entered STN: 19970327

Last Updated on STN: 19970327

Entered Medline: 19970314

AB This open-label, multicenter study of depressed men and women > or = 65 years old was conducted at 18 European hospitals to evaluate the safety, efficacy, and clinical acceptability of venlafaxine in elderly depressed patients during 1 year. Patients received venlafaxine orally as 25-mg tablets two or three times daily for up to 12 months. Dosages were titrated upward during the first 15 days and then maintained between 50 and 150 mg/day. Safety was assessed on the basis of study events, vital signs, electrocardiograms tracings, and laboratory determinations. Efficacy was assessed using the Montgomery-Asberg Depression Rating Scale (MADRS), the Clinical Global Impressions (CGI) scale, and the Hospital Anxiety and Depression scale. Patients' subjective ratings of the drug's tolerability and efficacy were collected. Study events were reported by 62% of patients. Few clinically or statistically significant changes occurred in vital signs or electrocardiogram or laboratory findings. No serious study events, including three deaths, were considered unexpected given the nature of the population and the length of treatment. Most patients (81%) believed they had no side effects. Clinical response was achieved in 67% of patients by month 2 (as measured by improvement on the CGI) and by 64% of patients by month 3 (as measured by improvement on the MADRS), suggesting that venlafaxine demonstrates antidepressant efficacy. Eighty-five (73%) patients were still in the study after 6 months and 77 (66%) were still participating at 12 months. Overall, most patients (80%) felt much or very much improved at the end of the study. Venlafaxine was safe, effective, and clinically acceptable treatment for depression in elderly patients.

CT Check Tags: Female; Male

Aged

Aged, 80 and over

*Antidepressive Agents, Second-Generation: AE, adverse effects

Antidepressive Agents, Second-Generation: TU, therapeutic use

Blood Pressure

*Cyclohexanols: AE, adverse effects

Cyclohexanols: TU, therapeutic use

*Depression: DT, drug therapy

Electrocardiography

Humans
 Research Support, Non-U.S. Gov't
 Sampling Studies
 Severity of Illness Index
 Time Factors
 Treatment Outcome

RN 93413-69-5 (venlafaxine)

CN 0 (Antidepressive Agents, Second-Generation); 0 (Cyclohexanols)

L91 ANSWER 98 OF 313 MEDLINE on STN

ACCESSION NUMBER: 96350144 MEDLINE

DOCUMENT NUMBER: PubMed ID: 8764759

TITLE: A novel approach to the pharmacology of analgesics.

AUTHOR: Raffa R B

CORPORATE SOURCE: RW Johnson Pharmaceutical Research Institute, Spring House, Pennsylvania, USA.

SOURCE: American journal of medicine, (1996 Jul 31) 101 (1A) 40S-46S. Ref: 33

Journal code: 0267200. ISSN: 0002-9343.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

General Review; (REVIEW)

(REVIEW, TUTORIAL)

LANGUAGE: English

FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals

ENTRY MONTH: 199609

ENTRY DATE: Entered STN: 19960924

Last Updated on STN: 19960924

Entered Medline: 19960913

AB To date in the United States when a patient has presented with a complaint of **pain** requiring some form of pharmacologic relief, the physician has had the choice of two broad classes of drugs: peripherally acting (i.e., NSAID) or centrally acting (i.e., opioid) analgesics. The **antidepressant monoamine reuptake inhibitors**, particularly when combined with an opioid analgesic, have also proven efficacious in treating certain types of **pain** conditions. A new approach, available for almost 20 years in Europe and recently approved for use in the United States, is the centrally acting synthetic analgesic tramadol HCl. Preclinical evidence suggests that tramadol produces its antinociceptive effect in animals and analgesic effect in humans through a complementary dual mechanism of action. One mechanism relates to its weak affinity for mu-opioid receptors (6,000-fold less than morphine, 100-fold less than d-propoxyphene, 10-fold less than codeine, and equivalent to dextromethorphan). A metabolite (O-desmethyltramadol; M1) binds to opioid receptors with a greater affinity than the parent compound and could contribute to this component. However, in most animal tests and human clinical trials, the analgesic effect of tramadol is only partially blocked by the opioid antagonist naloxone, suggesting an important nonopioid mechanism. This nonopioid mechanism possibly relates to an increase in central neuronal synaptic levels of two neurotransmitters, 5-hydroxytryptamine (5-HT; **serotonin**) and **norepinephrine**. The opioid and nonopioid mechanisms appear to combine in a supra-additive manner in several tests of antinociception, but only in an additive or even counteracting manner in measures of adverse-effect liability. In sum, the apparent dual mechanism of action of tramadol suggests a possible new approach to **pain** relief.

CT *Analgesics, Opioid: PD, pharmacology

Drug Synergism

Humans

***Pain: DT, drug therapy**

Stereoisomerism

***Tramadol: PD, pharmacology**

RN 27203-92-5 (Tramadol)

CN 0 (Analgesics, Opioid)

L91 ANSWER 99 OF 313 MEDLINE on STN

ACCESSION NUMBER: 97004338 MEDLINE

DOCUMENT NUMBER: PubMed ID: 8851649

TITLE: Venlafaxine in depressed geriatric outpatients: an open-label clinical study.

AUTHOR: Khan A; Rudolph R; Baumel B; Ferguson J; Ryan P; Shrivastava R

CORPORATE SOURCE: Northwest Psychiatric Institute, Kirkland, WA 98034, USA.

SOURCE: Psychopharmacology bulletin, (1995) 31 (4) 753-8.

Journal code: 0101123. ISSN: 0048-5764.

PUB. COUNTRY: United States

DOCUMENT TYPE: (CLINICAL TRIAL)

Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199612

ENTRY DATE: Entered STN: 19970128

Last Updated on STN: 19970128

Entered Medline: 19961205

AB A 12-month open-label clinical trial was conducted to evaluate patient acceptance and safety of venlafaxine, a novel antidepressant, in ambulatory geriatric depressed patients. The sample consisted of 58 depressed patients aged 65 years and older who needed long-term antidepressant treatment. The setting was multiple study sites in California, Florida, New York, Utah, and Washington. All patients took venlafaxine; 52 qualified for the intent-to-treat analysis, and 24 completed 12 months of treatment. Repeated-measures analysis of variance within subjects showed significant improvements in Clinical Global Impressions severity and improvement, Modified Symptom Checklist, and Quality of Life Questionnaire scores. One patient developed a rash that was judged to be a serious drug-related side effect. The most common side effects were headache (n = 25), nausea (n = 21), insomnia (n = 18), dry mouth (n = 18), and sweating (n = 18). The results demonstrate the safety and patient acceptance of venlafaxine in depressed geriatric outpatients for acute and maintenance treatment.

CT Check Tags: Female; Male

Aged

Antidepressive Agents, Second-Generation: AE, adverse effects

***Antidepressive Agents, Second-Generation: TU, therapeutic use**

Cyclohexanols: AE, adverse effects

***Cyclohexanols: TU, therapeutic use**

***Depression: DT, drug therapy**

Depression: PX, psychology

Humans

Psychiatric Status Rating Scales

Research Support, Non-U.S. Gov't

RN 93413-69-5 (venlafaxine)

CN 0 (Antidepressive Agents, Second-Generation); 0 (Cyclohexanols)

L91 ANSWER 100 OF 313 MEDLINE on STN

ACCESSION NUMBER: 96094180 MEDLINE

DOCUMENT NUMBER: PubMed ID: 7491403

TITLE: Venlafaxine: measuring the onset of antidepressant action.

AUTHOR: Derivan A; Entsuah A R; Kikta D
CORPORATE SOURCE: Wyeth-Ayerst Research, Radnor, PA, USA.
SOURCE: Psychopharmacology bulletin, (1995) 31 (2) 439-47.
Journal code: 0101123. ISSN: 0048-5764.
PUB. COUNTRY: United States
DOCUMENT TYPE: (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199601
ENTRY DATE: Entered STN: 19960125
Last Updated on STN: 19960125
Entered Medline: 19960104

AB Venlafaxine, a new antidepressant, inhibits reuptake of norepinephrine and serotonin without appreciable effects on histaminergic, alpha-adrenergic, or cholinergic systems. Pharmacologically the drug is unique: the half-life is short and it exerts both rapid and prolonged beta-adrenergic desensitization after single doses in a rodent model. Venlafaxine has been thought to possess a rapid onset of clinical antidepressant action. Accordingly, two clinical studies in which moderate amounts of venlafaxine were given aggressively were reviewed to examine aspects of the drug's onset of action. Three statistical methodologies were employed--traditional analysis of depression scale scores, pattern analysis based on timing and persistence of response, and survival analysis of sustained response. All three methods showed venlafaxine to have significant effects early in the course of therapy. In addition, venlafaxine is the first drug to meet criteria for early onset using the pattern analysis methodology. Depressed patients aggressively treated with venlafaxine show significant benefit on or before Day 7 of treatment using traditional methods of analysis as well as survival analysis of sustained response.

CT **Antidepressive Agents: TU, therapeutic use**
*Cyclohexanols: PD, pharmacology
*Cyclohexanols: TU, therapeutic use
 ***Depression: DT, drug therapy**
 Follow-Up Studies
 Humans
 Placebo Effect
*Serotonin Uptake Inhibitors: PD, pharmacology
*Serotonin Uptake Inhibitors: TU, therapeutic use
 Time Factors
 Treatment Outcome

RN **93413-69-5 (venlafaxine)**
CN 0 (Antidepressive Agents); 0 (Cyclohexanols); 0 (Serotonin Uptake Inhibitors)

L91 ANSWER 101 OF 313 MEDLINE on STN
ACCESSION NUMBER: 95246629 MEDLINE
DOCUMENT NUMBER: PubMed ID: 7729333
TITLE: Venlafaxine. A review of its pharmacology and therapeutic potential in depression.
AUTHOR: Holliday S M; Benfield P
CORPORATE SOURCE: Adis International Limited, Auckland, New Zealand.
SOURCE: Drugs, (1995 Feb) 49 (2) 280-94. Ref: 61
Journal code: 7600076. ISSN: 0012-6667.
PUB. COUNTRY: New Zealand
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)

LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 199506
 ENTRY DATE: Entered STN: 19950608
 Last Updated on STN: 19950608
 Entered Medline: 19950601

AB Venlafaxine is a phenylethylamine derivative which facilitates neurotransmission in the brain by blocking presynaptic reuptake of serotonin (5-hydroxytryptamine: 5-HT) and noradrenaline (norepinephrine). Clinical data from patients with major depression are consistent with the favourable efficacy and tolerability profile of venlafaxine predicted by pharmacodynamic studies. In patients with major depression, venlafaxine 75 to 375 mg/day administered for 6 weeks was significantly more effective than placebo, and at least as effective as imipramine, clomipramine, trazodone or fluoxetine. Venlafaxine is well tolerated, being associated with fewer anticholinergic and CNS adverse effects than tricyclic antidepressants. Unlike the tricyclic antidepressants, venlafaxine does not appear to significantly affect cardiac conduction; although there have been a few reports of modest increases in blood pressure, particularly after high doses of the drug. In conclusion, wider clinical experience is required to better characterise and confirm potential advantages of venlafaxine compared with other antidepressant agents. These advantages may include a rapid onset of action and reduced propensity to cause anticholinergic effects and cardiotoxicity compared with tricyclic antidepressants. Nevertheless, at this stage venlafaxine offers a more attractive treatment option than tricyclic antidepressants for patients with major depression, primarily because of its good overall tolerability profile.

CT Check Tags: Comparative Study
 Animals

Antidepressive Agents, Second-Generation: PK, pharmacokinetics
 Antidepressive Agents, Second-Generation: PD, pharmacology
 *Antidepressive Agents, Second-Generation: TU, therapeutic use
 Cardiovascular System: DE, drug effects
 *Central Nervous System: DE, drug effects
 Cyclohexanols: PK, pharmacokinetics
 Cyclohexanols: PD, pharmacology
 *Cyclohexanols: TU, therapeutic use
 *Depression: DT, drug therapy
 Dosage Forms
 Dose-Response Relationship, Drug
 Drug Interactions
 Humans
 *Synaptic Transmission: DE, drug effects

RN 93413-69-5 (venlafaxine)

CN 0 (Antidepressive Agents, Second-Generation); 0 (Cyclohexanols); 0 (Dosage Forms)

L91 ANSWER 102 OF 313 MEDLINE on STN
 ACCESSION NUMBER: 95029410 MEDLINE
 DOCUMENT NUMBER: PubMed ID: 7942885
 TITLE: Venlafaxine marketed as antidepressant.
 AUTHOR: Anonymous
 SOURCE: American journal of hospital pharmacy, (1994 Jul 1) 51 (13) 1606.
 Journal code: 0370474. ISSN: 0002-9289.
 PUB. COUNTRY: United States
 DOCUMENT TYPE: News Announcement
 LANGUAGE: English

FILE SEGMENT: Priority Journals
ENTRY MONTH: 199411
ENTRY DATE: Entered STN: 19941222
Last Updated on STN: 19941222
Entered Medline: 19941121
CT *Antidepressive Agents, Second-Generation: PD, pharmacology
*Cyclohexanols: PD, pharmacology
Depression: DT, drug therapy
Humans
*Serotonin Uptake Inhibitors: PD, pharmacology
Tablets
RN 93413-69-5 (venlafaxine)
CN 0 (Antidepressive Agents, Second-Generation); 0 (Cyclohexanols); 0
(Serotonin Uptake Inhibitors); 0 (Tablets)

L91 ANSWER 103 OF 313 MEDLINE on STN
ACCESSION NUMBER: 95159997 MEDLINE
DOCUMENT NUMBER: PubMed ID: 7856622
TITLE: Venlafaxine: a heterocyclic antidepressant.
COMMENT: Comment in: Am J Health Syst Pharm. 1995 Jul
15;52(14):1573-4. PubMed ID: 7552908
AUTHOR: Ellingrod V L; Perry P J
CORPORATE SOURCE: College of Pharmacy, University of Iowa, Iowa City
52242-0123.
SOURCE: American journal of hospital pharmacy, (1994 Dec 15) 51
(24) 3033-46. Ref: 32
Journal code: 0370474. ISSN: 0002-9289.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199503
ENTRY DATE: Entered STN: 19950322
Last Updated on STN: 19960306
Entered Medline: 19950316

AB The pharmacology, pharmacokinetics, and clinical efficacy of venlafaxine hydrochloride, a new antidepressant, are described. Venlafaxine inhibits the reuptake of serotonin, norepinephrine, and, to a lesser extent, dopamine. In animal models, it does not significantly inhibit muscarinic, histaminic, or adrenergic receptor activity and does not inhibit monoamine oxidase. Venlafaxine is rapidly absorbed and metabolized in the liver to its active metabolite, O-desmethylvenlafaxine (ODV). Time to peak concentration is one to two hours for the parent compound and four to five hours for ODV. The pharmacokinetics of venlafaxine might be dose-dependent, although pharmacokinetic studies have had conflicting results. The major route of elimination is renal; thus, patients with renal dysfunction may require lower doses. In double-blind, placebo-controlled trials of venlafaxine for maintenance therapy, venlafaxine has shown effective antidepressant activity in severely ill patients with major depression. Antidepressant effectiveness may be apparent within two weeks; this finding needs to be replicated. The dosage is 75-375 mg/day administered in two or three divided doses. The strength of the antidepressant response may be correlated with increasing dosage. Nausea is the most commonly reported adverse drug reaction (ADR). Others include somnolence, dizziness, dry mouth, and sweating. All ADRs have commonly occurred at the beginning of therapy and decreased with time. Overall, venlafaxine is well tolerated. Venlafaxine is as

effective as other available antidepressants. It may cause fewer anticholinergic, antihistaminic, and antiadrenergic ADRs and may have a quicker onset of therapeutic action than existing antidepressants.

CT Check Tags: Comparative Study

***Antidepressive Agents, Second-Generation**

Antidepressive Agents, Second-Generation: PK, pharmacokinetics

Antidepressive Agents, Second-Generation: PD, pharmacology

Clinical Trials, Phase II

Clinical Trials, Phase III

***Cyclohexanols**

Cyclohexanols: PK, pharmacokinetics

Cyclohexanols: PD, pharmacology

Depression: DT, drug therapy

Drug Interactions

Humans

Research Support, Non-U.S. Gov't

***Serotonin Uptake Inhibitors**

Serotonin Uptake Inhibitors: PK, pharmacokinetics

Serotonin Uptake Inhibitors: PD, pharmacology

RN 93413-69-5 (venlafaxine)

CN 0 (Antidepressive Agents, Second-Generation); 0 (Cyclohexanols); 0 (Serotonin Uptake Inhibitors)

L91 ANSWER 104 OF 313 MEDLINE on STN

ACCESSION NUMBER: 88263285 MEDLINE

DOCUMENT NUMBER: PubMed ID: 3387523

TITLE: An open-label, variable-dose study of WY-45,030 (venlafexine) in depressed outpatients.

AUTHOR: Goldberg H L; Finnerty R

SOURCE: Psychopharmacology bulletin, (1988) 24 (1) 198-9.
Journal code: 0101123. ISSN: 0048-5764.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 198808

ENTRY DATE: Entered STN: 19900308
Last Updated on STN: 19900308
Entered Medline: 19880809

CT Check Tags: Female; Male

Adult

Aged

***Antidepressive Agents: TU, therapeutic use**

***Cyclohexanols: TU, therapeutic use**

***Depression: DT, drug therapy**

Humans

Middle Aged

Outpatients

Research Support, Non-U.S. Gov't

RN 93413-69-5 (venlafaxine)

CN 0 (Antidepressive Agents); 0 (Cyclohexanols)

L91 ANSWER 105 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 1

ACCESSION NUMBER: 2005:493589 HCAPLUS

DOCUMENT NUMBER: 143:43777

TITLE: Preparation of pyridin-4-ylamines useful in the treatment of neuropathic pain

INVENTOR(S): Lim, Jongwon; Boueres, Julia K.; Munoz, Benito; Pracitto, Richard; Stock, Nicholas; Venkatraman,

PATENT ASSIGNEE(S): Shankar
 SOURCE: Merck & Co., Inc., USA
 PCT Int. Appl., 59 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005051915	A1	20050609	WO 2004-US38669	20041118
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW			
RW:	BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG			

PRIORITY APPLN. INFO.: US 2003-524734P P 20031121

OTHER SOURCE(S): MARPAT 143:43777

AB Title compds. I [R1-4 = H, halo, alkyl, etc.; R5-8 = H, alkyl, etc.; X = alkylene, O, S, SO₂, etc.] are prepared For instance, II is prepared from 9-chloroacridine and 2-amino-5-diethylaminopentane (phenol, Et₃N, 120°, 1 h) as a yellow oil. In a 3H-GABA_A receptor assay, I exhibit IC₅₀ values < 10 µM. I are useful in the treatment of, e.g., schizophrenia, anxiety, depression, bipolar disorders, and panic, as well as in the treatment of pain. The present invention is also directed to the use of triazolo-pyridazine compds. that selectively bind to α_{2δ}-1 subunit of Ca channels [no data].

IC ICM C07D215-00

ICS C07D219-00; A61K031-435; A61K031-47

CC 27-16 (Heterocyclic Compounds (One Hetero Atom))

Section cross-reference(s): 1, 63

IT Mental disorder

(**depression**; preparation of pyridin-4-ylamines useful in treatment of neuropathic pain)

IT **Nervous system agents**

(**noradrenaline reuptake inhibitors**;

preparation of pyridin-4-ylamines useful in treatment of neuropathic pain)

IT Alzheimer's disease

Amnesia

Analgesics

Anti-Alzheimer's agents

Anticonvulsants

Antidepressants

Antiparkinsonian agents

Antipsychotics

Anxiety

Anxiolytics

Drug withdrawal

Eating disorders

Epilepsy

Human

Pain

Parkinson's disease
Schizophrenia
Sleep disorders

(preparation of pyridin-4-ylamines useful in treatment of neuropathic pain)

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 106 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 2

ACCESSION NUMBER: 2005:34615 HCAPLUS

DOCUMENT NUMBER: 142:107432

TITLE: Combination of serotonin reuptake inhibitors and norepinephrine reuptake inhibitors for the treatment of depression

INVENTOR(S): Marek, Gerard J.; Giller, Earl L.; Ramey, Tanya S.; Gibbs, Megan A.; Wong, Erik H. F.; Marshall, Robert C.

PATENT ASSIGNEE(S): Pfizer Inc., USA

SOURCE: U.S. Pat. Appl. Publ., 15 pp., Cont.-in-part of U.S. Ser. No. 602,447.

CODEN: USXXCO

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 4

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2005009927	A1	20050113	US 2004-860721	20040603
US 2002107249	A1	20020808	US 2002-55663	20020123
US 2004102440	A1	20040527	US 2003-602447	20030624
WO 2005023265	A1	20050317	WO 2004-IB2864	20040902

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

NL 1026989 A1 20050310 NL 2004-1026989 20040908

PRIORITY APPLN. INFO.: US 2002-55663 A2 20020123
US 2002-392893P P 20020701
US 2003-602447 A2 20030624
US 2003-501275P P 20030909
US 2004-538898P P 20040123
US 2004-540696P P 20040130
US 1999-141968P P 19990701
US 1999-144131P P 19990716
US 1999-158256P P 19991006
US 1999-170381P P 19991213
US 2000-599213 A3 20000622
US 2004-769018 A 20040130
US 2004-860721 A 20040603

OTHER SOURCE(S): MARPAT 142:107432

AB The invention is directed in one embodiment to pharmaceutical compns. and methods for treating depression in a mammal. To a mammal in need of such

treatment are administered: (i) at least one serotonin reuptake inhibitor (e.g. sertraline) or pharmaceutically acceptable salt thereof; and (ii) at least one norepinephrine reuptake inhibitor [e.g. (S,S)-reboxetine] or pharmaceutically acceptable salt thereof.

IC ICM A61K031-137

INCL 514651000

CC 1-11 (Pharmacology)

Section cross-reference(s): 63

ST **serotonin norepinephrine reuptake**

inhibitor combination antidepressant; sertraline reboxetine combination depression treatment

IT 5-HT antagonists

(5-HT_{1B}; **serotonin reuptake inhibitor-norepinephrine reuptake inhibitor** combination for treatment of depression)

IT Mental disorder

(bipolar disorder; **serotonin reuptake inhibitor-norepinephrine reuptake inhibitor** combination for treatment of depression)

IT Development, mammalian postnatal

(child, pediatric depression and child abuse-induced depression; **serotonin reuptake inhibitor-norepinephrine reuptake inhibitor** combination for treatment of depression)

IT Brain

(corpus striatum; **serotonin reuptake inhibitor-norepinephrine reuptake inhibitor** combination for treatment of depression)

IT Human immunodeficiency virus

(depression in patients infected with; **serotonin reuptake inhibitor-norepinephrine reuptake inhibitor** combination for treatment of depression)

IT Parkinson's disease

(depression in; **serotonin reuptake inhibitor-norepinephrine reuptake inhibitor** combination for treatment of depression)

IT Mental disorder

(depression; **serotonin reuptake inhibitor-norepinephrine reuptake inhibitor** combination for treatment of depression)

IT Brain

(diencephalon; **serotonin reuptake inhibitor-norepinephrine reuptake inhibitor** combination for treatment of depression)

IT Fertility

(disorder, depression in infertile women; **serotonin reuptake inhibitor-norepinephrine reuptake inhibitor** combination for treatment of depression)

IT Neurotransmission

(dopaminergic; **serotonin reuptake inhibitor-norepinephrine reuptake inhibitor** combination for treatment of depression)

IT Heart, disease

(infarction, depression after; **serotonin reuptake inhibitor-norepinephrine reuptake inhibitor** combination for treatment of depression)

IT Mental disorder

(major depression; **serotonin reuptake inhibitor-norepinephrine reuptake inhibitor** combination for treatment of depression)

IT Mental disorder
(melancholy; **serotonin reuptake inhibitor-norepinephrine reuptake inhibitor** combination for treatment of depression)

IT Brain
(midbrain; **serotonin reuptake inhibitor-norepinephrine reuptake inhibitor** combination for treatment of depression)

IT Analgesics
(neuropathic pain; **serotonin reuptake inhibitor-norepinephrine reuptake inhibitor** combination for treatment of depression)

IT Pain
(neuropathic; **serotonin reuptake inhibitor-norepinephrine reuptake inhibitor** combination for treatment of depression)

IT Nerve, disease
(neuropathy, neuropathic pain; **serotonin reuptake inhibitor-norepinephrine reuptake inhibitor** combination for treatment of depression)

IT Mental disorder
(neurotic depression, major depression with; **serotonin reuptake inhibitor-norepinephrine reuptake inhibitor** combination for treatment of depression)

IT Neurotransmission
(noradrenergic; **serotonin reuptake inhibitor-norepinephrine reuptake inhibitor** combination for treatment of depression)

IT Transport proteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**norepinephrine transporter; serotonin reuptake inhibitor-norepinephrine reuptake inhibitor** combination for treatment of depression)

IT Mental disorder
(postpartum depression; **serotonin reuptake inhibitor-norepinephrine reuptake inhibitor** combination for treatment of depression)

IT Mental disorder
(psychosis, psychotic depression; **serotonin reuptake inhibitor-norepinephrine reuptake inhibitor** combination for treatment of depression)

IT Antipsychotics
(psychotic depression; **serotonin reuptake inhibitor-norepinephrine reuptake inhibitor** combination for treatment of depression)

IT Biological transport
(**reuptake; serotonin reuptake inhibitor-norepinephrine reuptake inhibitor** combination for treatment of depression)

IT 5-HT reuptake inhibitors
Antidepressants
Combination chemotherapy
Drug delivery systems

Human

(serotonin reuptake inhibitor-
norepinephrine reuptake inhibitor
combination for treatment of depression)

IT Transport proteins

RL: BSU (Biological study, unclassified); BIOL (Biological study)
(serotonin transporter; serotonin reuptake
inhibitor-norepinephrine reuptake
inhibitor combination for treatment of depression)

IT Neurotransmission

(serotonergic; serotonin reuptake
inhibitor-norepinephrine reuptake
inhibitor combination for treatment of depression)

IT Brain, disease

(stroke, depression after; serotonin reuptake
inhibitor-norepinephrine reuptake
inhibitor combination for treatment of depression)

IT 51-61-6, Dopamine, biological studies

RL: BSU (Biological study, unclassified); BIOL (Biological study)
(reuptake; serotonin reuptake
inhibitor-norepinephrine reuptake
inhibitor combination for treatment of depression)

IT 50-67-9, Serotonin, biological studies 51-41-2, Norepinephrine
135416-43-2, β -CIT

RL: BSU (Biological study, unclassified); BIOL (Biological study)
(serotonin reuptake inhibitor-
norepinephrine reuptake inhibitor
combination for treatment of depression)

IT 10262-69-8, Maprotiline 14028-44-5, Amoxapine 54739-18-3, Fluvoxamine
54910-89-3, Fluoxetine 71620-89-8 79617-96-2, Sertraline 98819-76-2
361343-19-3, Elzasonan 635724-54-8 635724-55-9 823801-55-4
823801-56-5 823801-57-6 823801-58-7 823801-59-8 823801-60-1

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL
(Biological study); USES (Uses)

(serotonin reuptake inhibitor-
norepinephrine reuptake inhibitor
combination for treatment of depression)

L91 ANSWER 107 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 10

ACCESSION NUMBER: 2004:817651 HCAPLUS

DOCUMENT NUMBER: 141:332206

TITLE: Preparation of biaryl substituted 6-membered
heterocycles as sodium channel blockersINVENTOR(S): Chakravarty, Prasun K.; Fisher, Michael H.; Parsons,
William H.; Liang, Jun; Zhou, Bishan

PATENT ASSIGNEE(S): Merck & Co., Inc., USA

SOURCE: PCT Int. Appl., 125 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004084824	A2	20041007	WO 2004-US8532	20040319
WO 2004084824	A3	20050331		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH,
CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD,

GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
 LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI,
 NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY,
 TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
 RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ,
 BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE,
 ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI,
 SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN,
 TD, TG

PRIORITY APPLN. INFO.:

US 2003-456312P

P 20030324

OTHER SOURCE(S):

MARPAT 141:332206

AB The title biaryl substituted pyridine, pyrimidine and pyrazine compds. [I or II; H-1 = (un)substituted pyridyl, pyrimidyl, pyrazinyl; H-2 = (un)substituted pyridyl, pyrimidyl, pyrazinyl; R4, R5 = H, alkyl, alkoxy, aryloxy, etc.; R6-R8 = H, alkyl, cycloalkyl, alkoxy, etc.] which are sodium channel blockers useful for the treatment of pain (no data), were prepared E.g., a 2-step synthesis of III, starting from 2-bromo-6-methylpyridine and 3-bromophenylboronic acid, was given. Claimed pharmaceutical compns. comprise an effective amount of the instant compds. I, either alone, or in combination with one or more therapeutically active compds., and a pharmaceutically acceptable carrier. Methods of treating conditions associated with, or caused by, sodium channel activity, including, for example, acute pain, chronic pain, visceral pain, inflammatory pain, neuropathic pain, epilepsy, irritable bowel syndrome, depression, anxiety, multiple sclerosis, and bipolar disorder, comprise administering an effective amount of the present compds., either alone, or in combination with one or more other therapeutically active compds.

IC ICM A61K

CC 28-16 (Heterocyclic Compounds (More Than One Hetero Atom))
 Section cross-reference(s): 1, 63

IT Nervous system agents

(noradrenaline reuptake inhibitors,
 co-drugs; preparation of biaryl substituted 6-membered heterocycles as
 sodium channel blockers for treatment or prevention of pain in
 combination with other therapeutic agents)

L91 ANSWER 108 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 11

ACCESSION NUMBER: 2004:392439 HCAPLUS

DOCUMENT NUMBER: 140:400095

TITLE: Stereoisomers of p-hydroxy-milnacipran, and therapeutic use

INVENTOR(S): Rariy, Roman V.; Heffernan, Michael; Buchwald, Stephen L.; Swager, Timothy M.

PATENT ASSIGNEE(S): Collegium Pharmaceutical, Inc., USA

SOURCE: PCT Int. Appl., 163 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 4

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004039320	A2	20040513	WO 2003-US33681	20031022
WO 2004039320	A3	20040624		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
 CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
 GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,

LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM,
 PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN,
 TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW
 RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,
 KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES,
 FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR,
 BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

CA 2503381 AA 20040513 CA 2003-2503381 20031022
 US 2004142904 A1 20040722 US 2003-691465 20031022
 EP 1578719 A2 20050928 EP 2003-776524 20031022

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
 IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK

PRIORITY APPLN. INFO.:

US 2002-421640P P 20021025
 US 2002-423062P P 20021101
 US 2003-445142P P 20030205
 WO 2003-US33681 W 20031022

OTHER SOURCE(S): MARPAT 140:400095

AB The invention relates generally to the enantiomers of p-hydroxymilnacipran or congeners thereof. Biol. assays revealed that racemic p-hydroxymilnacipran is approx. equipotent in inhibiting serotonin and norepinephrine uptake (IC₅₀ = 28.6 nM for norepinephrine, IC₅₀ = 21.7 nM for serotonin). Interestingly, (+)-p-hydroxymilnacipran is a more potent inhibitor of norepinephrine uptake than serotonin uptake (IC₅₀ = 10.3 nM for norepinephrine, IC₅₀ = 22 nM for serotonin). In contrast, (-)-p-hydroxymilnacipran is a more potent inhibitor of serotonin uptake compared to norepinephrine uptake (IC₅₀ = 88.5 nM for norepinephrine, IC₅₀ = 40.3 nM for serotonin). The invention also relates to salts and prodrug forms of the above compds. In certain embodiments, the compds. of the invention and a pharmaceutically acceptable excipient are combined to prepare a formulation for administration to a patient. Finally, the invention relates to methods of treating mammals suffering from various afflictions, e.g., depression, chronic pain, or fibromyalgia, comprising administering to a mammal in need thereof a therapeutically effective amount of a compound of the invention. Compound preparation is included.

IC ICM A61K

CC 1-11 (Pharmacology)

Section cross-reference(s): 25, 63

IT **Mental disorder**

(**depression**; p-hydroxymilnacipran stereoisomers, therapeutic use, and use with other agents)

IT **Mental disorder**

(**neurotic depression**; p-hydroxymilnacipran stereoisomers, therapeutic use, and use with other agents)

IT 50-02-2, Dexamethasone 50-22-6, Corticosterone 50-23-7, Hydrocortisone
 50-24-8, Prednisolone 50-33-9, Phenylbutazone, biological studies
 50-47-5, Desipramine 50-48-6, Amitriptyline 50-49-7, Imipramine
 50-52-2, Thioridazine 50-53-3, Chlorpromazine, biological studies
 50-55-5, Reserpine 50-78-2, Aspirin 51-63-8, Dextroamphetamine sulfate
 52-26-6, Morphinehydrochloride 52-86-8, Haloperidol 53-03-2,
 Prednisone 53-06-5, Cortisone 53-86-1, Indomethacin 57-27-2,
 Morphine, biological studies 57-41-0, Phenytoin 57-42-1, Meperidine
 57-53-4, Meprobamate 58-08-2, Caffeine, biological studies 58-25-3,
 Chlordiazepoxide 58-39-9, Perphenazine 58-46-8, Tetrabenazine
 58-94-6, Thiazide 59-92-7, Levodopa, biological studies 61-68-7,
 Mefenamic acid 62-44-2, Phenacetin 68-88-2, Hydroxyzine 69-23-8,
 Fluphenazine 72-69-5, Nortriptyline 73-31-4, Melatonin 76-41-5,
 Oxymorphone 76-42-6, Oxycodone 76-57-3, Codeine 76-99-3, Methadone
 77-67-8, Ethosuximide 78-44-4, Carisoprodol 83-98-7, Orphenadrine
 89-57-6, Mesalamine 99-66-1, Valproic acid 103-90-2, Acetaminophen

113-15-5, Ergotamine 113-45-1, Methylphenidate 113-53-1, Dothiepin
117-89-5, Trifluoperazine 119-36-8, Methylsalicylate 125-28-0,
Dihydrocodeine 125-29-1, Hydrocodone 129-03-3, Cyproheptadine
134-49-6, Phenmetrazine 138-56-7, Trimethobenzamide 298-46-4,
Carbamazepine 300-62-9, Amphetamine 302-40-9, Benactyzine 303-49-1,
Clomipramine 303-53-7, Cyclobenzaprine 315-72-0, Opipramol 321-64-2,
Tacrine 357-56-2, Dextromoramide 357-70-0, Galantamine 359-83-1,
Pentazocine 361-37-5, Methysergid(e 364-62-5, Metoclopramide
378-44-9, Betamethasone 427-00-9, Desomorphine 437-38-7, Fentanyl
438-60-8, Protriptyline 439-14-5, Diazepam 466-99-9, Hydromorphone
469-62-5, Dextropropoxyphene 509-60-4, Dihydromorphine 511-12-6,
Dihydroergotamine 525-66-6, Propranolol 532-03-6, Methocarbamol
537-46-2, Methamphetamine 552-94-3, Salsalate 555-30-6, Methyl dopa
599-79-1, Sulfasalazine 604-75-1, Oxazepam 634-03-7, Phendimetrazine
739-71-9, Trimipramine 765-30-0, Aminocyclopropane 768-94-5,
Amantadine 846-49-1, Lorazepam 846-50-4, Temazepam 1406-18-4,
Vitamin E 1622-61-3, Clonazepam 1665-48-1, Metaxalone 1668-19-5,
Doxepin 1977-10-2, Loxapine 2016-36-6, Choline salicylate, biological
studies 2062-78-4, Pimozide 2152-34-3, Pemoline 3313-26-6,
Thiothixene 3861-76-5, Clonitazene 3900-31-0, Fludiazepam 3964-81-6,
Azatadine 4205-90-7, Clonidine 4350-09-8, Oxitriptan 4419-39-0,
Beclomethasone 4498-32-2, Dibenzeperin 4757-55-5, Dimetacrine
5104-49-4, Flurbiprofen 5118-29-6, Melitracen 5560-72-5, Iprindole
5786-21-0, Clozapine 7416-34-4, Molindone 9001-62-1, Lipase
9001-75-6, Pepsin 10262-69-8, Maprotiline 10321-12-7, Propizepine
14028-44-5, Amoxapine 15301-93-6, Tofenacin 15307-79-6, Diclofenac
sodium 15574-96-6, Pizotifen 15687-27-1, Ibuprofen 15722-48-2,
Olsalazine 17617-23-1, Flurazepam 19794-93-5, Trazodone 19982-08-2,
Memantine 21256-18-8, Oxaprozin 21730-16-5, Metapramine 22071-15-4,
Ketoprofen 22204-53-1, Naproxen 22232-71-9, Mazindol 22494-42-4,
Diflunisal 23047-25-8, Lofepramine 23887-31-2, Clorazepate
24166-13-0, Cloxazolam 24219-97-4, Mianserin 24526-64-5, Nomifensine
24701-51-7, Demexiptiline 25614-03-3, Bromocriptine 25905-77-5,
Minaprine 26171-23-3, Tolmetin 26629-87-8, Oxaflozane 27060-91-9,
Flutazolam 27203-92-5, Tramadol 28860-95-9, Carbidopa 28911-01-5,
Triazolam 28981-97-7, Alprazolam 29218-27-7, Toloxatone 29679-58-1,
Fenoprofen 29975-16-4, Estazolam 31721-17-2, Quinupramine
31842-01-0, Indoprofen 33671-46-4, Clotiazepam 34911-55-2, Bupropion
35941-65-2, Butriptyline 36322-90-4, Piroxicam 36505-84-7, Buspirone
36735-22-5, Quazepam 38194-50-2, Sulindac 41340-25-4, Etodolac
42200-33-9, Nadolol 42408-82-2, Butorphanol 42924-53-8, Nabumetone
43200-80-2, Zopiclone 46817-91-8, Viloxazine 51012-32-9, Tiapride
51022-69-6, Amcinonide 51234-28-7, Benoxaprofen 51322-75-9, Tizanidine
51333-22-3, Budesonide 52485-79-7, Buprenorphine 53608-75-6,
Pancrelipase 53648-55-8, Dezocine 54739-18-3, Fluvoxamine
54910-89-3, Fluoxetine 56775-88-3, Zimeldine 59729-33-8, Citalopram
59859-58-4, Femoxetine 60142-96-3, Gabapentin 60762-57-4, Pirlindole
61869-08-7, Paroxetine 68693-11-8, Modafinil 71195-57-8,
Bicifadine 71320-77-9, Moclobemide 71620-89-8, Reboxetine
74050-98-9, Ketanserin 74103-06-3, Ketorolac 76584-70-8 78499-27-1,
Bermoprofen 79617-96-2, Sertraline 82626-48-0, Zolpidem 83015-26-3,
Atomoxetine 83366-66-9, Nefazodone 83928-76-1, Gepirone 84371-65-3,
Mifepristone 85650-52-8, Mirtazapine 87051-43-2, Ritanserin
87691-91-6, Tiaspirone 88150-42-9, Amlodipine 89565-68-4, Tropisetron
89796-99-6, Aceclofenac 91374-21-9, Ropinirole 93413-69-5, Venlafaxine
95847-70-4, Ipsapirone 97240-79-4, Topiramate 99614-02-5, Ondansetron
99755-59-6, Rotigotine 102518-79-6, Huperzine A 103628-46-2,
Sumatriptan 104632-26-0, Pramipexole 106266-06-2, Risperidone
106650-56-0, Sibutramine 109889-09-0, Granisetron 112924-45-5,

Dexanabinol 115956-12-2, Dolasetron 116539-59-4, Duloxetine
 120014-06-4, Donepezil 121679-13-8, Naratriptan 123040-69-7, Azasetron
 123441-03-2, Rivastigmine 128196-01-0, Escitalopram 129722-12-9,
 Aripiprazole 132449-46-8, Lesopitron 132539-06-1, Olanzapine
 139264-17-8, Zolmitriptan 139755-83-2, Sildenafil 144034-80-0,
 Rizatriptan 146939-27-7, Ziprasidone 148553-50-8, Pregabalin
 154323-57-6, Almotriptan 158747-02-5, Frovatriptan 162011-90-7,
 Rofecoxib 169590-42-5, Celecoxib 181695-72-7, Valdecoxib
 198470-84-7, Parecoxib 325715-02-4, Indiplon 686766-17-6
 686766-17-6D, derivs. 688319-36-0, Adomexetine
 RL: PAC (Pharmacological activity); THU (Therapeutic
 use); BIOL (Biological study); USES (Uses)
 (p-hydroxymilnacipran stereoisomers, therapeutic use, and use with
 other agents)

L91 ANSWER 109 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 12

ACCESSION NUMBER: 2004:80490 HCAPLUS

DOCUMENT NUMBER: 140:122820

TITLE: Treatment of **depression secondary**
 to **pain** using milnacipran and other
 monoamine reuptake inhibitors

INVENTOR(S): Rao, Srinivas G.; Kranzler, Jay D.

PATENT ASSIGNEE(S): Cypress Bioscience, Inc., USA

SOURCE: PCT Int. Appl., 33 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 5

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004009069	A1	20040129	WO 2003-US23088	20030724
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2493490	AA	20040129	CA 2003-2493490	20030724
EP 1545489	A1	20050629	EP 2003-748971	20030724
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
PRIORITY APPLN. INFO.:			US 2002-398676P	P 20020724
			US 2003-443035P	P 20030128
			WO 2003-US23088	W 20030724

AB The invention discloses the methods for the prevention or treatment of
 atypical **depression secondary to pain** (**DSP**). The method generally involves administering an effective
 amount of a monoamine re uptake inhibitor to treat or prevent symptoms of
DSP. In a preferred embodiment, a therapeutically effective amount
 of a dual **serotonin norepinephrine reuptake**
inhibitor (SRNI) compound of a specific type, or a pharmaceutically
 acceptable salt thereof is administered. The most preferred SNRI compds.
 are non-tricyclic SNRIs, wherein serotonin reuptake inhibition is greater

than norepinephrine reuptake inhibition; and **NSRIs**, wherein norepinephrine reuptake inhibition is greater than serotonin reuptake inhibition. The most preferred compound is milnacipran or a bioequivalent or pharmaceutically acceptable salt thereof. Other preferred compds. are duloxetine and venlafaxine or a bioequivalent or pharmaceutically acceptable salt thereof. In yet another embodiment, a therapeutically effective amount of a non-tricyclic **triple reuptake inhibitor** ('TRI') compound of a specific type, or a pharmaceutically acceptable salt thereof, is administered. The TRI compds. are characterized by their ability to block the reuptake (and, hence, increase central concns. of) the three primary brain monoamines: serotonin, noradrenaline, and dopamine.

IC ICM A61K031-165
 CC 1-11 (Pharmacology)
 ST **depression pain** monoamine reuptake milnacipran
 duloxetine venlafaxine; **serotonin norepinephrine**
 dopamine **reuptake inhibitor** milnacipran duloxetine
 venlafaxine depression
 IT Glutamate antagonists
 (NMDA antagonists; treatment of **depression secondary**
 to **pain** using milnacipran and other monoamine reuptake
 inhibitors)
 IT **Pain**
 (abdominal; treatment of **depression secondary** to
pain using milnacipran and other monoamine reuptake inhibitors)
 IT Disease, animal
 (back **pain**; treatment of **depression**
secondary to **pain** using milnacipran and other
 monoamine reuptake inhibitors)
 IT Body, anatomical
 (back, disease, **pain**; treatment of **depression**
secondary to **pain** using milnacipran and other
 monoamine reuptake inhibitors)
 IT **Pain**
 (back; treatment of **depression secondary** to
pain using milnacipran and other monoamine reuptake inhibitors)
 IT **Pain**
 (chest **pain**; treatment of **depression**
secondary to **pain** using milnacipran and other
 monoamine reuptake inhibitors)
 IT **Pain**
 (chronic; treatment of **depression secondary** to
pain using milnacipran and other monoamine reuptake inhibitors)
 IT **Mental disorder**
 (**depression**; treatment of **depression**
secondary to **pain** using milnacipran and other
 monoamine reuptake inhibitors)
 IT Head
 (face, **pain**; treatment of **depression**
secondary to **pain** using milnacipran and other
 monoamine reuptake inhibitors)
 IT Nerve, disease
 (neuropathy, **pain**; treatment of **depression**
secondary to **pain** using milnacipran and other
 monoamine reuptake inhibitors)
 IT Abdomen, disease
 Headache
 Neck, anatomical
 Thorax

(**pain**; treatment of **depression secondary**
to **pain** using milnacipran and other monoamine reuptake
inhibitors)

IT Body, anatomical
(pelvis, **pain**; treatment of **depression**
secondary to **pain** using milnacipran and other
monoamine reuptake inhibitors)

IT Biological transport
(reuptake, norepinephrine reuptake inhibitor; treatment of
depression secondary to **pain** using
milnacipran and other monoamine reuptake inhibitors)

IT 5-HT reuptake inhibitors
Antidepressants
Drug delivery systems
Epilepsy
Human
Seizures
(treatment of **depression secondary** to **pain**
using milnacipran and other monoamine reuptake inhibitors)

IT 50-67-9, Serotonin, biological studies 51-41-2, Norepinephrine
51-61-6, Dopamine, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(treatment of **depression secondary** to **pain**
using milnacipran and other monoamine reuptake inhibitors)

IT 765-30-0D, Aminocyclopropane, derivative 92623-85-3D, Milnacipran,
derivative 106650-56-0, Sibutramine
RL: **PAC (Pharmacological activity)**; **THU (Therapeutic**
use); BIOL (Biological study); USES (Uses)
(treatment of **depression secondary** to **pain**
using milnacipran and other monoamine reuptake inhibitors)

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 110 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 18
ACCESSION NUMBER: 2003:757508 HCAPLUS
DOCUMENT NUMBER: 139:255389
TITLE: **Norepinephrine- and serotonin-**
reuptake inhibitors for treating
visceral pain syndromes
INVENTOR(S): Rao, Srinivas G.; Kranzler, Jay D.
PATENT ASSIGNEE(S): Cypress Bioscience, Inc., USA
SOURCE: PCT Int. Appl., 127 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003077897	A1	20030925	WO 2003-US8155	20030317
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW			
RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES,			

FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR,
 BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
 CA 2479350 AA 20030925 CA 2003-2479350 20030317
 US 2003203055 A1 20031030 US 2003-391110 20030317
 EP 1485078 A1 20041215 EP 2003-744697 20030317
 R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
 IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK
 JP 2005526079 T2 20050902 JP 2003-575950 20030317
 NO 2004004345 A 20041203 NO 2004-4345 20041013
 PRIORITY APPLN. INFO.: US 2002-364531P P 20020315
 WO 2003-US8155 W 20030317

OTHER SOURCE(S): MARPAT 139:255389

AB The invention provides a method for treating a visceral pain syndrome in a mammal. The method includes administering an effective amount of a selective **norepinephrine (NE)-serotonin (5-HT) reuptake inhibitor (NSRI)**, e.g., milnacipran.

IC ICM A61K031-165

ICS A61K031-00; A61P025-00

CC 1-11 (Pharmacology)

ST **norepinephrine serotonin reuptake**

inhibitor visceral pain syndrome treatment; milnacipran visceral pain syndrome treatment

IT 5-HT agonists

(5-HT1; **norepinephrine-serotonin reuptake**

inhibitors for treating visceral pain syndromes, and use with other agents)

IT 5-HT antagonists

(5-HT2A; **norepinephrine-serotonin reuptake**

inhibitors for treating visceral pain syndromes, and use with other agents)

IT 5-HT antagonists

(5-HT3; **norepinephrine-serotonin reuptake**

inhibitors for treating visceral pain syndromes, and use with other agents)

IT Glutamate antagonists

(NMDA antagonists; **norepinephrine-serotonin**

reuptake inhibitors for treating visceral pain syndromes, and use with other agents)

IT Biliary tract

(Oddi's sphincter, dysfunction; **norepinephrine-**

serotonin reuptake inhibitors for treating

visceral pain syndromes, and use with other agents)

IT Muscle

(abcess; **norepinephrine-serotonin reuptake**

inhibitors for treating visceral pain syndromes, and use with other agents)

IT Abdomen

(abdominal bloating and pain; **norepinephrine-**

serotonin reuptake inhibitors for treating

visceral pain syndromes, and use with other agents)

IT Antimigraine agents

(abdominal migraine; **norepinephrine-serotonin**

reuptake inhibitors for treating visceral pain syndromes, and use with other agents)

IT Nervous system

(adrenergic; **norepinephrine-serotonin**

reuptake inhibitors for treating visceral pain syndromes, and use with other agents)

IT Disease, animal

- (aerophagia; **norepinephrine-serotonin reuptake inhibitors** for treating visceral pain syndromes, and use with other agents)
- IT Heterocyclic compounds
 RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (antidepressant; **norepinephrine-serotonin reuptake inhibitors** for treating visceral pain syndromes, and use with other agents)
- IT Fatigue, biological
 (antifatigue agent; **norepinephrine-serotonin reuptake inhibitors** for treating visceral pain syndromes, and use with other agents)
- IT Intestine
 (anus, functional anorectal pain syndrome; **norepinephrine-serotonin reuptake inhibitors** for treating visceral pain syndromes, and use with other agents)
- IT Natural products, pharmaceutical
 RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (belladonna, alkaloid; **norepinephrine-serotonin reuptake inhibitors** for treating visceral pain syndromes, and use with other agents)
- IT Alkaloids, biological studies
 RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (belladonna; **norepinephrine-serotonin reuptake inhibitors** for treating visceral pain syndromes, and use with other agents)
- IT Gastrointestinal agents
 (bulk-forming agents; **norepinephrine-serotonin reuptake inhibitors** for treating visceral pain syndromes, and use with other agents)
- IT Catecholamines, biological studies
 RL: BSU (Biological study, unclassified); BIOL (Biological study)
 (catecholaminergic agents; **norepinephrine-serotonin reuptake inhibitors** for treating visceral pain syndromes, and use with other agents)
- IT Nervous system
 (cholinergic; **norepinephrine-serotonin reuptake inhibitors** for treating visceral pain syndromes, and use with other agents)
- IT Disease, animal
 (coccygodynia; **norepinephrine-serotonin reuptake inhibitors** for treating visceral pain syndromes, and use with other agents)
- IT Intestine, disease
 (constipation; **norepinephrine-serotonin reuptake inhibitors** for treating visceral pain syndromes, and use with other agents)
- IT Disease, animal
 (cryptitis; **norepinephrine-serotonin reuptake inhibitors** for treating visceral pain syndromes, and use with other agents)
- IT Bladder, disease
 Inflammation
 (cystitis, interstitial; **norepinephrine-serotonin reuptake inhibitors** for treating visceral pain syndromes, and use with other agents)

IT Viscera
(disease, pain; **norepinephrine-serotonin reuptake inhibitors** for treating visceral pain syndromes, and use with other agents)

IT Disease, animal
(dyschezia; **norepinephrine-serotonin reuptake inhibitors** for treating visceral pain syndromes, and use with other agents)

IT Gallbladder
(dysfunction; **norepinephrine-serotonin reuptake inhibitors** for treating visceral pain syndromes, and use with other agents)

IT Disease, animal
(dysphagia; **norepinephrine-serotonin reuptake inhibitors** for treating visceral pain syndromes, and use with other agents)

IT Disease, animal
(dyssynergia; **norepinephrine-serotonin reuptake inhibitors** for treating visceral pain syndromes, and use with other agents)

IT Intestine, disease
(fecal incontinence; **norepinephrine-serotonin reuptake inhibitors** for treating visceral pain syndromes, and use with other agents)

IT Disease, animal
(fissure; **norepinephrine-serotonin reuptake inhibitors** for treating visceral pain syndromes, and use with other agents)

IT Dyspepsia
(functional; **norepinephrine-serotonin reuptake inhibitors** for treating visceral pain syndromes, and use with other agents)

IT Electrolytes, biological
(glucose-electrolyte solution; **norepinephrine-serotonin reuptake inhibitors** for treating visceral pain syndromes, and use with other agents)

IT Digestive tract
(gut analgesics; **norepinephrine-serotonin reuptake inhibitors** for treating visceral pain syndromes, and use with other agents)

IT Vein, disease
(hemorrhoid; **norepinephrine-serotonin reuptake inhibitors** for treating visceral pain syndromes, and use with other agents)

IT Intestine, disease
(inflammatory; **norepinephrine-serotonin reuptake inhibitors** for treating visceral pain syndromes, and use with other agents)

IT Intestine, disease
(irritable bowel syndrome; **norepinephrine-serotonin reuptake inhibitors** for treating visceral pain syndromes, and use with other agents)

IT Headache
(migraine, abdominal; **norepinephrine-serotonin reuptake inhibitors** for treating visceral pain syndromes, and use with other agents)

IT Pain
Thorax
(non-cardiac chest pain; **norepinephrine-serotonin**

reuptake inhibitors for treating visceral pain syndromes, and use with other agents)
 IT Neuromuscular **blocking** agents
 (nondepolarizing; **norepinephrine-serotonin reuptake inhibitors** for treating visceral pain syndromes, and use with other agents)
 IT Anti-inflammatory agents
 (nonsteroidal; **norepinephrine-serotonin reuptake inhibitors** for treating visceral pain syndromes, and use with other agents)
 IT 5-HT **reuptake inhibitors**
 Analgesics
 Anti-inflammatory agents
 Anti-ischemic agents
 Anticonvulsants
Antidepressants
 Antidiarrheals
 Antiulcer agents
 Appetite **depressants**
 Calcium channel **blockers**
 Cholinergic **antagonists**
 Diarrhea
 Drug delivery systems
 Gastrointestinal agents
 Hypnotics and Sedatives
 Ischemia
 Laxatives
 Nervous system stimulants
 (**norepinephrine-serotonin reuptake inhibitors** for treating visceral pain syndromes, and use with other agents)
 IT Corticosteroids, biological studies
 Glucocorticoids
 Opioids
 Paraffin oils
 RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (**norepinephrine-serotonin reuptake inhibitors** for treating visceral pain syndromes, and use with other agents)
 IT Testis
 (orchialgia; **norepinephrine-serotonin reuptake inhibitors** for treating visceral pain syndromes, and use with other agents)
 IT Drugs
 (oxicams; **norepinephrine-serotonin reuptake inhibitors** for treating visceral pain syndromes, and use with other agents)
 IT Penis
 (penile pain; **norepinephrine-serotonin reuptake inhibitors** for treating visceral pain syndromes, and use with other agents)
 IT Body, anatomical
 (perineum, perineal pain; **norepinephrine-serotonin reuptake inhibitors** for treating visceral pain syndromes, and use with other agents)
 IT Disease, animal
 (proctalgia fugax; **norepinephrine-serotonin reuptake inhibitors** for treating visceral pain

syndromes, and use with other agents)

IT Inflammation
Prostate gland, disease
(prostatitis; **norepinephrine-serotonin reuptake inhibitors** for treating visceral pain syndromes, and use with other agents)

IT Prostate gland
(prostatodynia; **norepinephrine-serotonin reuptake inhibitors** for treating visceral pain syndromes, and use with other agents)

IT Intestine
(rectum, functional anorectal pain syndrome; **norepinephrine-serotonin reuptake inhibitors** for treating visceral pain syndromes, and use with other agents)

IT Intestine
(rectum, rectal pain; **norepinephrine-serotonin reuptake inhibitors** for treating visceral pain syndromes, and use with other agents)

IT Nervous system agents
(serotonergic-noradrenergic and catecholaminergic; **norepinephrine-serotonin reuptake inhibitors** for treating visceral pain syndromes, and use with other agents)

IT Ulcer
(solitary rectal; **norepinephrine-serotonin reuptake inhibitors** for treating visceral pain syndromes, and use with other agents)

IT Muscle relaxants
(spasmolytics; **norepinephrine-serotonin reuptake inhibitors** for treating visceral pain syndromes, and use with other agents)

IT Feces
(stool softeners; **norepinephrine-serotonin reuptake inhibitors** for treating visceral pain syndromes, and use with other agents)

IT Biological transport
(uptake; **norepinephrine-serotonin reuptake inhibitors** for treating visceral pain syndromes, and use with other agents)

IT Urethra
(urethral syndrome; **norepinephrine-serotonin reuptake inhibitors** for treating visceral pain syndromes, and use with other agents)

IT Inflammation
Vagina, disease
(vaginitis, cyclic vulvovaginitis; **norepinephrine-serotonin reuptake inhibitors** for treating visceral pain syndromes, and use with other agents)

IT Disease, animal
(visceral pain; **norepinephrine-serotonin reuptake inhibitors** for treating visceral pain syndromes, and use with other agents)

IT Pain
(visceral; **norepinephrine-serotonin reuptake inhibitors** for treating visceral pain syndromes, and use with other agents)

IT Reproductive organ
(vulva, dysesthetic vulvodynia; **norepinephrine-serotonin reuptake inhibitors** for treating

- visceral pain syndromes, and use with other agents)
- IT Reproductive organ
(vulva, essential vulvodynia; **norepinephrine-serotonin reuptake inhibitors** for treating visceral pain syndromes, and use with other agents)
- IT Reproductive organ
(vulva, vulvar dermatoses; **norepinephrine-serotonin reuptake inhibitors** for treating visceral pain syndromes, and use with other agents)
- IT Reproductive organ
(vulva, vulvar papillomatosis; **norepinephrine-serotonin reuptake inhibitors** for treating visceral pain syndromes, and use with other agents)
- IT Reproductive organ
(vulva, vulvar vestibulitis; **norepinephrine-serotonin reuptake inhibitors** for treating visceral pain syndromes, and use with other agents)
- IT Adrenoceptor agonists
(α -; **norepinephrine-serotonin reuptake inhibitors** for treating visceral pain syndromes, and use with other agents)
- IT 77-10-1, Phencyclidine
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(PCP-site **antagonist**; **norepinephrine-serotonin reuptake inhibitors** for treating visceral pain syndromes, and use with other agents)
- IT 50-99-7, D-Glucose, biological studies
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(glucose-electrolyte solution; **norepinephrine-serotonin reuptake inhibitors** for treating visceral pain syndromes, and use with other agents)
- IT 56-86-0, L-Glutamic acid, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(glutamate-site **antagonist**; **norepinephrine-serotonin reuptake inhibitors** for treating visceral pain syndromes, and use with other agents)
- IT 56-40-6, Glycine, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(glycine-site **antagonist**; **norepinephrine-serotonin reuptake inhibitors** for treating visceral pain syndromes, and use with other agents)
- IT 9001-66-5, Monoamine oxidase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**inhibitors**; **norepinephrine-serotonin reuptake inhibitors** for treating visceral pain syndromes, and use with other agents)
- IT 50-67-9, **Serotonin**, biological studies 51-41-2, **Norepinephrine**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**norepinephrine-serotonin reuptake inhibitors** for treating visceral pain syndromes, and use with other agents)
- IT 50-06-6, Phenobarbital, biological studies 51-55-8, , Atropine, biological studies 55-63-0, Nitroglycerin 57-27-2, Morphine, biological studies 57-41-0, Phenytoin 59-66-5, Acetazolamide 59-92-7, biological studies 63-42-3, , Lactose 67-52-7D, 2,4,6(1H,3H,5H)-Pyrimidinetrione, derivs. 69-72-7D, Salicylic acid, salicylates, biological studies 76-57-3, Codeine 77-09-8,

Phenolphthalein 77-19-0, Dicyclomine 77-67-8, Ethosuximide 79-09-4,
 Propionic acid, biological studies 91-20-3D, Naphthalene,
 naphthylalkanones 91-40-7D, Fenamic acid, fenamates 99-66-1
 101-31-5, Hyoscyamine 120-72-9D, Indole, derivs. 123-30-8D,
 p-Aminophenol, derivs. 125-33-7, , Primidone 137-58-6, Lidocaine
 288-13-1D, Pyrazole, derivs. 298-46-4, Carbamazepine 300-62-9,
 Amphetamine 439-14-5, Valium 1622-61-3, , Clonazepam 8029-99-0,
 Paregoric 8063-16-9, , Psyllium 12794-10-4, Benzodiazepine
 19794-93-5, Trazodone 27203-92-5, Tramadol 43200-80-2, Zopiclone
 51322-75-9, Tizanidine 53179-11-6, Loperamide 60142-96-3, , Gabapentin
 68693-11-8, Modafinil 82626-48-0, Zolpidem 83150-76-9, , Octreotide
 84057-84-1, Lamotrigine 89565-68-4, Tropisetron 92623-85-3,
 Milnacipran 93390-81-9, Fosphenytoin 97240-79-4, Topiramate
 104632-26-0, , Pramipexole 106650-56-0, Sibutramine 122852-42-0, ,
 Alosetron 145158-71-0, Tegaserod 148553-50-8, Pregabalin
 216382-88-6, Imidazopyridine
 RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL
 (Biological study); USES (Uses)

(**norepinephrine-serotonin reuptake**

inhibitors for treating visceral pain syndromes, and use with
 other agents)

REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS
 RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 111 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 19
 ACCESSION NUMBER: 2003:511137 HCAPLUS
 DOCUMENT NUMBER: 139:47219
 TITLE: Methods of treating fibromyalgia syndrome, chronic
 fatigue syndrome and pain with dual **serotonin**
-norepinephrine reuptake
inhibitor
 INVENTOR(S): Rao, Srinivas G.; Kranzler, Jay D.
 PATENT ASSIGNEE(S): Cypress Bioscience, Inc., USA
 SOURCE: PCT Int. Appl., 75 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 5
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003053426	A1	20030703	WO 2002-US40976	20021219
W: CA, US				
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT,				
LU, MC, NL, PT, SE, SI, SK, TR				
US 2003130353	A1	20030710	US 2001-28547	20011219
US 6602911	B2	20030805		
PRIORITY APPLN. INFO.:			US 2001-28547	A1 20011219
			US 2001-14149	A2 20011105

OTHER SOURCE(S): MARPAT 139:47219

AB The present invention provides a method of treating, in a mammal, chronic
 fatigue syndrome (CFS), chronic fatigue syndrome (CFS) that is associated
 with depression, a combination of chronic fatigue syndrome (CFS) and
 fibromyalgia syndrome (FMS), fibromyalgia syndrome (FMS) associated with
depression, pain, and pain associated with
depression. The method includes administering a therapeutically
 effective amount of a dual **serotonin-norepinephrine**
reuptake inhibitor compound or a pharmaceutically

acceptable salt thereof.

IC ICM A61K031-135

CC 1-12 (Pharmacology)

ST fibromyalgia fatigue syndrome **serotonin norepinephrine reuptake inhibitor**

IT Pain

Skin, disease
(allodynia; treatment of fibromyalgia and chronic fatigue syndrome and pain with dual **serotonin-norepinephrine reuptake inhibitor**)

IT Brain
(cerebral cortex; treatment of fibromyalgia and chronic fatigue syndrome and pain with dual **serotonin-norepinephrine reuptake inhibitor**)

IT Fatigue, biological
(chronic fatigue syndrome; treatment of fibromyalgia and chronic fatigue syndrome and pain with dual **serotonin-norepinephrine reuptake inhibitor**)

IT Mental disorder
(**depression**; treatment of fibromyalgia and chronic fatigue syndrome and pain with dual **serotonin-norepinephrine reuptake inhibitor**)

IT Nerve, disease
(diabetic neuropathy; treatment of fibromyalgia and chronic fatigue syndrome and pain with dual **serotonin-norepinephrine reuptake inhibitor**)

IT Muscle, disease
(fibromyalgia; treatment of fibromyalgia and chronic fatigue syndrome and pain with dual **serotonin-norepinephrine reuptake inhibitor**)

IT Injury
(head; treatment of fibromyalgia and chronic fatigue syndrome and pain with dual **serotonin-norepinephrine reuptake inhibitor**)

IT Breathing (animal)
(hyperventilation; treatment of fibromyalgia and chronic fatigue syndrome and pain with dual **serotonin-norepinephrine reuptake inhibitor**)

IT Spinal cord, disease
(injury, traumatic; treatment of fibromyalgia and chronic fatigue syndrome and pain with dual **serotonin-norepinephrine reuptake inhibitor**)

IT Head, disease
(injury; treatment of fibromyalgia and chronic fatigue syndrome and pain with dual **serotonin-norepinephrine reuptake inhibitor**)

IT Intestine, disease
(irritable bowel syndrome; treatment of fibromyalgia and chronic fatigue syndrome and pain with dual **serotonin-norepinephrine reuptake inhibitor**)

IT Allergy
(multiple chemical sensitivity; treatment of fibromyalgia and chronic fatigue syndrome and pain with dual **serotonin-norepinephrine reuptake inhibitor**)

IT Ovarian cycle
(premenstrual syndrome; treatment of fibromyalgia and chronic fatigue syndrome and pain with dual **serotonin-norepinephrine reuptake inhibitor**)

IT Injury

(spinal cord, traumatic; treatment of fibromyalgia and chronic fatigue syndrome and pain with dual **serotonin-norepinephrine reuptake inhibitor**)

IT Joint, anatomical
(temporomandibular, dysfunction syndrome; treatment of fibromyalgia and chronic fatigue syndrome and pain with dual **serotonin-norepinephrine reuptake inhibitor**)

IT 5-HT reuptake inhibitors
Analgesics
Antiarthritics
Anticonvulsants
Antidepressants
Appetite **depressants**
Arthritis
Diabetes mellitus
Human
Multiple sclerosis
Muscle relaxants
Nervous system stimulants
Pain
Rheumatoid arthritis
(treatment of fibromyalgia and chronic fatigue syndrome and pain with dual **serotonin-norepinephrine reuptake inhibitor**)

IT 50-67-9, Serotonin, biological studies 51-41-2, Norepinephrine
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(treatment of fibromyalgia and chronic fatigue syndrome and pain with dual **serotonin-norepinephrine reuptake inhibitor**)

IT 57-27-2, Morphine, biological studies 59-92-7, L-DOPA, biological studies 76-57-3, Codeine 298-46-4, Carbamazepine 300-62-9, Amphetamine 439-14-5, Valium 4205-90-7, Clonidine 19794-93-5, Trazodone 27203-92-5, Tramadol 51322-75-9, Tizanidine 60142-96-3, Neurontin 92623-85-3, Milnacipran 104632-26-0, Pramipexole 106650-56-0, Sibutramine 148553-50-8, Pregabalin
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(treatment of fibromyalgia and chronic fatigue syndrome and pain with dual **serotonin-norepinephrine reuptake inhibitor**)

REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 112 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 20
ACCESSION NUMBER: 2003:376684 HCAPLUS
DOCUMENT NUMBER: 138:374216
TITLE: Selective **norepinephrine serotonin reuptake inhibitors** for treating fibromyalgia syndrome, chronic fatigue syndrome and pain
INVENTOR(S): Rao, Srinivas G.; Kranzler, Jay D.
PATENT ASSIGNEE(S): Cypress Bioscience, Inc., USA
SOURCE: PCT Int. Appl., 75 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 5
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003039598	A1	20030515	WO 2002-US35396	20021105
WO 2003039598	C1	20040603		
W: CA, US				
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR				
US 2003139476	A1	20030724	US 2001-14149	20011105
US 6635675	B2	20031021		
CA 2467356	AA	20030515	CA 2002-2467356	20021105
EP 1463528	A1	20041006	EP 2002-793880	20021105
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, CY, TR, BG, CZ, EE, SK				
PRIORITY APPLN. INFO.:			US 2001-14149	A 20011105
			WO 2002-US35396	W 20021105

OTHER SOURCE(S): MARPAT 138:374216

AB The present invention provides a method of treating, in a mammal, chronic fatigue syndrome (CFS), chronic fatigue syndrome (CFS) that is associated with depression, a combination of chronic fatigue syndrome (CFS) and fibromyalgia syndrome (FMS), fibromyalgia syndrome (FMS) associated with **depression, pain** and **pain** associated with **depression**. The method includes administering a therapeutically effective amount of a dual **serotonin norepinephrine reuptake inhibitor** compound or a pharmaceutically acceptable salt thereof. The effect of milnacipran in FMS animal and patients were examined

IC ICM A61K045-00
ICS A61K031-165; A61P025-00

CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 1

ST milnacipran **norepinephrine serotonin reuptake inhibitor**

IT Pain
(abdominal; selective **norepinephrine serotonin reuptake inhibitors** for treating fibromyalgia syndrome, chronic fatigue syndrome and pain)

IT Muscle, disease
(ache; selective **norepinephrine serotonin reuptake inhibitors** for treating fibromyalgia syndrome, chronic fatigue syndrome and pain)

IT Pain
Skin, disease
(allodynia; selective **norepinephrine serotonin reuptake inhibitors** for treating fibromyalgia syndrome, chronic fatigue syndrome and pain)

IT Disease, animal
(back pain, lower; selective **norepinephrine serotonin reuptake inhibitors** for treating fibromyalgia syndrome, chronic fatigue syndrome and pain)

IT Body, anatomical
(back, disease, pain, lower; selective **norepinephrine serotonin reuptake inhibitors** for treating fibromyalgia syndrome, chronic fatigue syndrome and pain)

IT Pain
(back, lower; selective **norepinephrine serotonin reuptake inhibitors** for treating fibromyalgia syndrome, chronic fatigue syndrome and pain)

IT Brain
(cerebral cortex; selective **norepinephrine serotonin**

- reuptake inhibitors** for treating fibromyalgia syndrome, chronic fatigue syndrome and pain)
- IT Fatigue, biological
(chronic fatigue syndrome; selective **norepinephrine serotonin reuptake inhibitors** for treating fibromyalgia syndrome, chronic fatigue syndrome and pain)
- IT Bladder, disease
Inflammation
(cystitis, interstitial cystitis; selective **norepinephrine serotonin reuptake inhibitors** for treating fibromyalgia syndrome, chronic fatigue syndrome and pain associated with)
- IT Mental disorder
(depression; selective **norepinephrine serotonin reuptake inhibitors** for treating fibromyalgia syndrome, chronic fatigue syndrome and pain associated with)
- IT Memory, biological
(disorder, impaired memory; selective **norepinephrine serotonin reuptake inhibitors** for treating fibromyalgia syndrome, chronic fatigue syndrome and pain associated with)
- IT Sleep disorders
(excessive sleep; selective **norepinephrine serotonin reuptake inhibitors** for treating fibromyalgia syndrome, chronic fatigue syndrome and pain associated with)
- IT Head
(face, myofascial face pain; selective **norepinephrine serotonin reuptake inhibitors** for treating fibromyalgia syndrome, chronic fatigue syndrome and pain)
- IT Muscle, disease
(fibromyalgia; selective **norepinephrine serotonin reuptake inhibitors** for treating fibromyalgia syndrome, chronic fatigue syndrome and pain)
- IT Injury
(head, closed head injury; selective **norepinephrine serotonin reuptake inhibitors** for treating fibromyalgia syndrome, chronic fatigue syndrome and pain associated with)
- IT Pain
(hyperalgesia; selective **norepinephrine serotonin reuptake inhibitors** for treating fibromyalgia syndrome, chronic fatigue syndrome and pain)
- IT Allergy
(hypersensitivity, multiple chemical sensitivity; selective **norepinephrine serotonin reuptake inhibitors** for treating fibromyalgia syndrome, chronic fatigue syndrome and pain associated with)
- IT Breathing (animal)
(hyperventilation; selective **norepinephrine serotonin reuptake inhibitors** for treating fibromyalgia syndrome, chronic fatigue syndrome and pain associated with)
- IT Eating disorders
(increased appetite; selective **norepinephrine serotonin reuptake inhibitors** for treating fibromyalgia syndrome, chronic fatigue syndrome and pain associated with)
- IT Head, disease
(injury, closed head injury; selective **norepinephrine serotonin reuptake inhibitors** for treating fibromyalgia syndrome, chronic fatigue syndrome and pain associated with)
- IT Spinal cord, disease
(injury; selective **norepinephrine serotonin reuptake inhibitors** for treating fibromyalgia syndrome, chronic fatigue syndrome and pain associated with)

syndrome, chronic fatigue syndrome and pain associated with)

IT Intestine, disease
 (irritable bowel syndrome; selective **norepinephrine serotonin reuptake inhibitors** for treating fibromyalgia syndrome, chronic fatigue syndrome and pain associated with)

IT Mental disorder
 (impaired mental concentration; selective **norepinephrine serotonin reuptake inhibitors** for treating fibromyalgia syndrome, chronic fatigue syndrome and pain associated with)

IT Disease, animal
 (malaise; selective **norepinephrine serotonin reuptake inhibitors** for treating fibromyalgia syndrome, chronic fatigue syndrome and pain associated with)

IT Mental disorder
 (memory disorder, impaired memory; selective **norepinephrine serotonin reuptake inhibitors** for treating fibromyalgia syndrome, chronic fatigue syndrome and pain associated with)

IT Mental disorder
 (mood-affecting; selective **norepinephrine serotonin reuptake inhibitors** for treating fibromyalgia syndrome, chronic fatigue syndrome and pain associated with)

IT Abdomen, disease
 Neck, anatomical
 Thorax
 (pain; selective **norepinephrine serotonin reuptake inhibitors** for treating fibromyalgia syndrome, chronic fatigue syndrome and pain)

IT Body, anatomical
 (pelvis, pain; selective **norepinephrine serotonin reuptake inhibitors** for treating fibromyalgia syndrome, chronic fatigue syndrome and pain)

IT Inflammation
 Pharynx, disease
 (pharyngitis; selective **norepinephrine serotonin reuptake inhibitors** for treating fibromyalgia syndrome, chronic fatigue syndrome and pain associated with)

IT Ovarian cycle
 (premenstrual syndrome; selective **norepinephrine serotonin reuptake inhibitors** for treating fibromyalgia syndrome, chronic fatigue syndrome and pain associated with)

IT Fatigue, biological
 Headache
 Human
 Neurotransmitter antagonists
 Pain
 (selective **norepinephrine serotonin reuptake inhibitors** for treating fibromyalgia syndrome, chronic fatigue syndrome and pain)

IT AIDS (disease)
 Arthritis
 Diabetes mellitus
 Fever and Hyperthermia
 Insomnia
 Multiple sclerosis
 Neoplasm
 Obesity
 Rheumatoid arthritis
 (selective **norepinephrine serotonin reuptake inhibitors** for treating fibromyalgia)

- syndrome, chronic fatigue syndrome and pain associated with)
- IT Analgesics
Anticonvulsants
Antidepressants
Appetite depressants
Hypnotics and Sedatives
Muscle relaxants
Nervous system stimulants
(selective **norepinephrine serotonin reuptake inhibitors** for treating fibromyalgia syndrome, chronic fatigue syndrome and pain with other active substances)
- IT Injury
(spinal cord; selective **norepinephrine serotonin reuptake inhibitors** for treating fibromyalgia syndrome, chronic fatigue syndrome and pain associated with)
- IT Synapse
(synaptosome; selective **norepinephrine serotonin reuptake inhibitors** for treating fibromyalgia syndrome, chronic fatigue syndrome and pain)
- IT Disease, animal
(temporomandibular joint; selective **norepinephrine serotonin reuptake inhibitors** for treating fibromyalgia syndrome, chronic fatigue syndrome and pain associated with)
- IT Joint, anatomical
(temporomandibular, disease; selective **norepinephrine serotonin reuptake inhibitors** for treating fibromyalgia syndrome, chronic fatigue syndrome and pain associated with)
- IT Lymph node, disease
(tender lymph nodes; selective **norepinephrine serotonin reuptake inhibitors** for treating fibromyalgia syndrome, chronic fatigue syndrome and pain associated with)
- IT 50-67-9, Serotonin, biological studies 51-41-2, **Norepinephrine**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(selective **norepinephrine serotonin reuptake inhibitors** for treating fibromyalgia syndrome, chronic fatigue syndrome and pain)
- IT 92623-85-3, Milnacipran
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(selective **norepinephrine serotonin reuptake inhibitors** for treating fibromyalgia syndrome, chronic fatigue syndrome and pain)
- IT 57-27-2, Morphine, biological studies 59-92-7, biological studies
76-57-3, Codeine 298-46-4, Carbamazepine 300-62-9, Amphetamine
439-14-5, Valium 4205-90-7, Clonidine 19794-93-5, Trazodone
27203-92-5, Tramadol 51322-75-9, Tizanidine 60142-96-3, Neurontin
104632-26-0, Pramipexole 106650-56-0, Sibutramine 148553-50-8,
Pregabalin
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(selective **norepinephrine serotonin reuptake inhibitors** for treating fibromyalgia syndrome, chronic fatigue syndrome and pain with other active substances)

REFERENCE COUNT: 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 113 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 26
ACCESSION NUMBER: 2002:905854 HCAPLUS

DOCUMENT NUMBER: 137:384744
 TITLE: Preparation of 3-(heteroaryloxy)propanamines as
serotonin and norepinephrine
reuptake inhibitors for treatment of
 pain
 INVENTOR(S): Gallagher, Peter Thaddeus; Rathmell, Richard Edmund;
 Fagan, Maria Ann
 PATENT ASSIGNEE(S): Eli Lilly and Company, USA
 SOURCE: PCT Int. Appl., 116 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002094262	A1	20021128	WO 2002-US11874	20020506
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2445010	AA	20021128	CA 2002-2445010	20020506
EP 1397129	A1	20040317	EP 2002-771578	20020506
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP 2004534037	T2	20041111	JP 2002-590979	20020506
US 2004176435	A1	20040909	US 2003-476137	20031023
PRIORITY APPLN. INFO.:			GB 2001-12122	A 20010518
			WO 2002-US11874	W 20020506

OTHER SOURCE(S): MARPAT 137:384744

AB Title compds. I [wherein A = O or S; X = (un)substituted Ph or thienyl; Y = (un)substituted benzothienyl, indolyl, or benzofuranyl; R1 and R2 = independently H or alkyl; and pharmaceutically acceptable salts thereof] were prepared as **serotonin and norepinephrine reuptake inhibitors** (no data). For example, (R)-(+)-3-chloro-1-phenyl-1-propanol was condensed with benzothiophen-7-ol in the presence of (4,4-dimethyl-1,1-dioxido-1,2,5-thiazolidin-2-yl)triphenylphosphonium in THF to give 7-[[[(1S)-3-chloro-1-phenylpropyl]oxy]benzothiophene (37%). Amination with methylamine in EtOH followed by conversion to the salt afforded II•oxalate. Solid phase synthetic methods were also presented. I are useful for the treatment of disorders associated with serotonin and norepinephrine dysfunction, such as depression, OCD, anxiety, memory loss, urinary incontinence, conduct disorders, ADHD, obesity, alcoholism, smoking cessation, and pain (no data).

IC ICM A61K031-40

ICS A61K031-34; A61K031-38; A61P025-00; C07D209-32; C07D209-42; C07D307-82; C07D307-83; C07D307-86

CC 27-9 (Heterocyclic Compounds (One Hetero Atom))
 Section cross-reference(s): 1

ST benzothienyloxypropanamine indolyloxypropanamine
 benzofuranyloxypropanamine prepn **serotonin**

norepinephrine reuptake inhibitor; pain
treatment heteroaryloxy propanamine prepn; urinary incontinence treatment
heteroaryloxy propanamine prepn; depression treatment heteroaryloxy
propanamine prepn

- IT Mental disorder
(attention deficit hyperactivity disorder; preparation of
(heteroaryloxy)propanamine **serotonin** and
norepinephrine reuptake inhibitors for
treatment of **depression**, urinary incontinence, **pain**
, and other CNS disorders)
- IT Mental disorder
(depression; preparation of (heteroaryloxy)propanamine **serotonin**
and **norepinephrine reuptake inhibitors**
for treatment of **depression**, urinary incontinence,
pain, and other CNS disorders)
- IT Behavior
(disorder; preparation of (heteroaryloxy)propanamine **serotonin** and
norepinephrine reuptake inhibitors for
treatment of **depression**, urinary incontinence, **pain**
, and other CNS disorders)
- IT Bladder, disease
(incontinence; preparation of (heteroaryloxy)propanamine **serotonin**
and **norepinephrine reuptake inhibitors**
for treatment of **depression**, urinary incontinence,
pain, and other CNS disorders)
- IT Adrenoceptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(noradrenergic; preparation of (heteroaryloxy)propanamine **serotonin**
and **norepinephrine reuptake inhibitors**
for treatment of **depression**, urinary incontinence,
pain, and other CNS disorders)
- IT Mental disorder
(obsession-compulsion; preparation of (heteroaryloxy)propanamine
serotonin and **norepinephrine reuptake**
inhibitors for treatment of **depression**, urinary
incontinence, **pain**, and other CNS disorders)
- IT Alcoholism
Amnesia
Analgesics
Antidepressants
Antiobesity agents
Anxiety
Anxiolytics
Cognition enhancers
Human
Nervous system agents
Obesity
Pain
Solid phase synthesis
(preparation of (heteroaryloxy)propanamine **serotonin** and
norepinephrine reuptake inhibitors for
treatment of **depression**, urinary incontinence, **pain**
, and other CNS disorders)
- IT 5-HT receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(preparation of (heteroaryloxy)propanamine **serotonin** and
norepinephrine reuptake inhibitors for
treatment of **depression**, urinary incontinence, **pain**
, and other CNS disorders)

IT Behavior

(smoking; preparation of (heteroaryloxy)propanamine **serotonin** and **norepinephrine reuptake inhibitors** for treatment of **depression**, urinary incontinence, **pain**, and other CNS disorders)

IT 450-88-4P, 2-Bromo-5-fluoroanisole 2513-49-7P, 5-Bromo-6,7-dihydrobenzothiophen-4(5H)-one 3610-02-4P, Benzothiophen-4-ol 4790-81-2P, 1-Benzofuran-7-ol 40570-64-7P, 3-Chloro-1-(2-thienyl)-1-propanone 56724-09-5P, 5-Methoxy-2-methylbenzaldehyde 59845-54-4P, 4-Methylbenzothiophen-7-ol 74266-68-5P, 3-Fluoro-2-methoxybenzaldehyde 74681-55-3P, 3-[Benzyl(methyl)amino]-1-phenyl-1-propanol 77898-35-2P, Benzothiophen-7-ol 88791-08-6P, Benzothien-7-yl methyl ether 88791-18-8P, 7-Methoxybenzothiophene-2-carbonitrile 92014-05-6P, 6-Methoxybenzothiophene-2-carbonitrile 94019-87-1P, 4-Cyano-7-hydroxybenzothiophene 96803-64-4P, 1-[(2,2-Diethoxyethyl)thio]-2-methoxybenzene 98015-07-7P, 4-Bromo-3-(1,3-dioxolan-2-yl)phenyl methyl ether 114133-36-7P, (S)-(-)-3-Iodo-1-phenyl-1-propanol 127073-84-1P, (R)-(+)-3-Iodo-1-phenyl-1-propanol 164071-55-0P, (1R)-3-Chloro-1-(2-thienyl)-1-propanol 170282-84-5P, 3-(1,3-Dioxolan-2-yl)-4-methylphenyl methyl ether 187543-87-9P, 2,3-Difluoro-6-methoxybenzaldehyde 217099-77-9P, 6-Hydroxybenzothiophene-2-carbonitrile 398456-80-9P, 4-Fluoro-2-methoxybenzenethiol 446873-57-0P, 5-(2-Fluoro-5-methoxybenzylidene)-2-thioxo-1,3-thiazolidin-4-one 476198-74-0P, 3-Methoxy-5-trifluoromethylbenzenethiol 476198-75-1P, 1-[(5-Fluoro-2-methoxyphenyl)thio]acetone 476198-76-2P, 1-[(2-Fluoro-5-methoxyphenyl)thio]acetone 476198-77-3P, 1-[(2,2-Diethoxyethyl)thio]-4-fluoro-2-methoxybenzene 476198-78-4P, 1-[(2,2-Diethoxyethyl)thio]-3-methoxy-5-trifluoromethylbenzene 476198-79-5P, 5-Fluorobenzothien-7-yl methyl ether 476198-80-8P, 4-Trifluoromethylbenzothien-6-yl methyl ether 476198-81-9P, 4-Fluoro-7-methoxybenzothiophene 476198-84-2P, 5-(3-Fluoro-2-methoxybenzylidene)-2-thioxo-1,3-thiazolidin-4-one 476198-86-4P, 5-(2-Methyl-5-methoxybenzylidene)-2-thioxo-1,3-thiazolidin-4-one 476198-88-6P, (2Z)-3-(2-Fluoro-5-methoxyphenyl)-2-mercapto-2-propenoic acid 476198-90-0P, (2Z)-3-(3-Fluoro-2-methoxyphenyl)-2-mercapto-2-propenoic acid 476198-91-1P, (2Z)-3-(2-Methyl-5-methoxyphenyl)-2-mercapto-2-propenoic acid 476198-92-2P, 4-Fluoro-7-methoxybenzothiophene-2-carboxylic acid 476198-93-3P, 4-Methyl-7-methoxybenzothiophene-2-carboxylic acid 476198-95-5P, 4-Methyl-7-methoxybenzothiophene 476198-96-6P, 5-Fluoro-4-methoxybenzothiophene 476198-97-7P, 5-Fluoro-4-methoxybenzothiophene-2-carboxylic acid 476198-98-8P, 7-Fluoro-4-methoxybenzothiophene 476198-99-9P, 2-(5-Fluoro-2-methoxyphenyl)-2-hydroxy-N,N-dimethylethanethioamide 476199-00-5P, N-(7-Fluoro-4-methoxybenzothien-2-yl)-N,N-dimethylamine 476199-01-6P, 7-Fluoro-4-methoxybenzothiophen-2(3H)-one 476199-02-7P, Methyl 7-fluoro-4-methoxybenzothiophene-2-carboxylate 476199-03-8P, 7-Fluoro-4-methoxybenzothiophene-2-carboxylic acid 476199-04-9P, 3-Chloro-4-fluoro-7-methoxybenzothiophene 476199-05-0P, (2E)-3-(2-Fluoro-5-methoxyphenyl)-2-propenoic acid 476199-06-1P, Methyl 3-chloro-4-fluoro-7-methoxybenzothiophene-2-carboxylate 476199-07-2P, 3-Chloro-4-fluoro-7-methoxybenzothiophene-2-carboxylic acid 476199-08-3P, 4-Fluoro-7-methoxy-3-methylbenzothiophene 476199-09-4P, 7-Fluoro-4-methoxy-3-methylbenzothiophene 476199-10-7P, 2-Fluoro-7-methoxybenzothiophene 476199-11-8P, 2-Fluoro-4-methoxybenzothiophene 476199-12-9P, 2-Iodo-7-methoxybenzothiophene 476199-13-0P, 4-Methoxybenzothiophene-2-carbonitrile 476199-15-2P, 4-Fluoro-7-methoxybenzothiophene-2-carbonitrile 476199-16-3P, 4-Fluoro-7-methoxybenzothiophene-2-carboxamide 476199-17-4P, 4-Cyano-7-methoxybenzothiophene 476199-18-5P, O-(2-Formyl-5-

methoxyphenyl) dimethylthiocarbamate 476199-19-6P, S-(2-Formyl-5-methoxyphenyl) dimethylthiocarbamate 476199-20-9P, 5-Fluorobenzothiophen-7-ol 476199-21-0P, 4-Trifluoromethylbenzothiophen-6-ol 476199-22-1P, 5-Fluorobenzothiophen-4-ol 476199-23-2P, 7-Fluorobenzothiophen-4-ol 476199-24-3P, 3-Chloro-4-fluorobenzothiophen-7-ol 476199-25-4P, 3-Methyl-4-fluorobenzothiophen-7-ol 476199-26-5P, 7-Fluoro-3-methylbenzothiophen-4-ol 476199-27-6P, 2-Fluorobenzothiophen-7-ol 476199-28-7P, 2-Fluorobenzothiophen-4-ol 476199-29-8P, 7-Hydroxybenzothiophene-2-carbonitrile 476199-30-1P, 4-Hydroxybenzothiophene-2-carbonitrile 476199-31-2P, 4-Fluoro-7-hydroxybenzothiophene-2-carbonitrile 476199-32-3P, 6-Fluorobenzothiophene-7-ol 476199-34-5P, 7-[(1S)-3-Chloro-1-phenylpropyl]oxy]benzothiophene 476199-35-6P, 4-[(1S)-3-Chloro-1-phenylpropyl]oxy]benzothiophene 476199-36-7P, 5-[(1S)-3-Chloro-1-phenylpropyl]oxy]benzothiophene 476199-37-8P, 6-[(1S)-3-Chloro-1-phenylpropyl]oxy]benzothiophene 476199-38-9P, 7-[(1S)-3-Chloro-1-phenylpropyl]oxy]-4-fluorobenzothiophene 476199-39-0P, 7-[(1S)-3-Chloro-1-phenylpropyl]oxy]-4-fluoro-3-methylbenzothiophene 476199-40-3P, 7-[(1S)-3-Chloro-1-phenylpropyl]oxy]-4-fluoro-3-chlorobenzothiophene 476199-41-4P, 7-[(1S)-3-Chloro-1-phenylpropyl]oxy]-4-methylbenzothiophene 476199-42-5P, 7-[(1S)-3-Chloro-1-phenylpropyl]oxy]-2-fluorobenzothiophene 476199-43-6P, 7-[(1S)-3-Chloro-1-phenylpropyl]oxy]-5-fluorobenzothiophene 476199-44-7P, 6-[(1S)-3-Chloro-1-phenylpropyl]oxy]-4-trifluoromethylbenzothiophene 476199-45-8P, 4-[(1S)-3-Chloro-1-phenylpropyl]oxy]-5-fluorobenzothiophene 476199-46-9P, 4-[(1S)-3-Chloro-1-phenylpropyl]oxy]-7-fluorobenzothiophene 476199-47-0P, 4-[(1S)-3-Chloro-1-phenylpropyl]oxy]-7-fluoro-3-methylbenzothiophene 476199-48-1P, 7-[(1S)-3-Chloro-1-phenylpropyl]oxy]benzothiophene-2-carbonitrile 476199-49-2P, 4-[(1S)-3-Chloro-1-phenylpropyl]oxy]benzothiophene-2-carbonitrile 476199-50-5P, 4-Cyano-7-[(1S)-3-chloro-1-phenylpropyl]oxy]benzothiophene 476199-53-8P, 4-[(1S)-3-Iodo-1-phenylpropyl]oxy]benzothiophene-2-carbonitrile 476199-54-9P, 7-[(1S)-3-Iodo-1-phenylpropyl]oxy]benzothiophene-2-carbonitrile 476199-56-1P, 4-Fluoro-7-[(1S)-3-iodo-1-phenylpropyl]oxy]benzothiophene-2-carbonitrile 476199-57-2P, 6-[(1S)-3-Iodo-1-phenylpropyl]oxy]benzothiophene-2-carbonitrile 476199-58-3P, 7-[(1S)-3-Iodo-1-phenylpropyl]oxy]-6-fluorobenzothiophene 476199-61-8P, 7-[(1S)-3-Chloro-1-(2-thienyl)propyl]oxy]benzothiophene 476199-62-9P, 7-[(1R)-3-Chloro-1-phenylpropyl]oxy]benzothiophene 476199-63-0P, 4-[(1R)-3-Chloro-1-phenylpropyl]oxy]benzothiophene 476199-64-1P, 5-[(1R)-3-Chloro-1-phenylpropyl]oxy]benzothiophene 476199-65-2P, 6-[(1R)-3-Chloro-1-phenylpropyl]oxy]benzothiophene 476199-66-3P, 7-[(1R)-3-Chloro-1-phenylpropyl]oxy]-4-fluorobenzothiophene 476199-67-4P, 7-[(1R)-3-Chloro-1-phenylpropyl]oxy]-4-fluoro-3-methylbenzothiophene 476199-68-5P, 7-[(1R)-3-Chloro-1-phenylpropyl]oxy]-4-fluoro-3-chlorobenzothiophene 476199-69-6P, 7-[(1R)-3-Chloro-1-phenylpropyl]oxy]-4-methylbenzothiophene 476199-70-9P, 7-[(1R)-3-Chloro-1-phenylpropyl]oxy]-2-fluorobenzothiophene 476199-71-0P, 4-[(1R)-3-Chloro-1-phenylpropyl]oxy]-2-fluorobenzothiophene 476199-72-1P, 7-[(1R)-3-Chloro-1-phenylpropyl]oxy]-5-fluorobenzothiophene 476199-73-2P, 6-[(1R)-3-Chloro-1-phenylpropyl]oxy]-4-trifluoromethylbenzothiophene 476199-74-3P, 4-[(1R)-3-Chloro-1-phenylpropyl]oxy]-5-fluorobenzothiophene 476199-75-4P, 4-[(1R)-3-Chloro-1-phenylpropyl]oxy]-7-fluorobenzothiophene 476199-76-5P, 4-[(1R)-3-Chloro-1-phenylpropyl]oxy]-7-fluoro-3-methylbenzothiophene 476199-77-6P, 7-[(R)-3-Chloro-1-phenylpropyl]oxy]benzothiophene-2-carbonitrile 476199-78-7P,

4-(((1R)-3-Chloro-1-phenylpropyl)oxy]benzothiophene-2-carbonitrile
 476199-79-8P, 4-Cyano-7-(((1R)-3-chloro-1-phenylpropyl)oxy]benzothiophene
 476199-83-4P, 7-(((1R)-3-Iodo-1-phenylpropyl)oxy]benzothiophene-2-
 carbonitrile 476199-84-5P, 4-(((1R)-3-Iodo-1-
 phenylpropyl)oxy]benzothiophene-2-carbonitrile 476199-86-7P,
 4-Fluoro-7-(((1R)-3-iodo-1-phenylpropyl)oxy]benzothiophene-2-carbonitrile
 476199-87-8P, 6-(((1R)-3-Iodo-1-phenylpropyl)oxy]benzothiophene-2-
 carbonitrile 476199-88-9P, 7-(((1R)-3-Iodo-1-phenylpropyl)oxy]-6-
 fluorobenzothiophene 476199-90-3P, Benzothiophene-7-thiol
 476199-91-4P, 1-[(Benzothien-7-yl)thio]-N-benzyl-N-methyl-3-
 phenylpropanamine 476199-92-5P, 3-[(Benzothienyl-4-yl)thio]-N-benzyl-N-
 methyl-3-phenyl-1-propanamine 476200-17-6P, (3S)-3-[(2-Cyanobenzothien-7-
 yl)oxy]-N-methyl-3-phenyl-1-propanamine

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT
 (Reactant or reagent)

(intermediate; preparation of (benzothienyloxy)propanamine **serotonin**
 and **norepinephrine reuptake inhibitors**

from thiophenols, phenylthioacetones, phenylmercaptopropenoic acids, or
 benzothiophenols)

IT 13523-92-7P, 1-Methyl-1H-indol-5-ol 475577-33-4P, 1-Methyl-1H-indol-7-ol
 475577-34-5P, 7-Benzyloxy-1-methyl-1H-indole 476199-51-6P,
 5-(((1S)-3-Chloro-1-phenylpropyl)oxy]-1-methyl-1H-indole 476199-52-7P,
 7-(((1S)-3-Chloro-1-phenylpropyl)oxy]-1H-indole 476199-59-4P,
 5-(((1S)-3-Iodo-1-phenylpropyl)oxy]-1-methyl-1H-indole 476199-60-7P,
 7-((1S)-3-Iodo-1-phenylpropoxy)benzofuran 476199-80-1P,
 7-(((1R)-3-Chloro-1-phenylpropyl)oxy]-1H-indole 476199-81-2P,
 4-(((1R)-3-Chloro-1-phenylpropyl)oxy]-1H-indole 476199-82-3P,
 5-(((1R)-3-Chloro-1-phenylpropyl)oxy]-1-methyl-1H-indole 476199-85-6P,
 5-(((1R)-3-Iodo-1-phenylpropyl)oxy]-1-methyl-1H-indole 476199-89-0P,
 7-((1R)-3-Iodo-1-phenylpropoxy)benzofuran 476200-68-7P 476200-69-8P,
 [(3R)-[(Benzofuran-4-yl)oxy]-3-phenylpropyl]-N-methylamine 476200-72-3P,
 [(3S)-[(Benzofuran-7-yl)oxy]-3-phenylpropyl]methylamine

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT
 (Reactant or reagent)

(intermediate; preparation of (heteroaryloxy)propanamine **serotonin**
 and **norepinephrine reuptake inhibitors**

for treatment of **depression**, urinary incontinence,
pain, and other CNS disorders)

IT 78-95-5, Chloroacetone 79-44-7, N,N-Dimethylcarbonyl chloride
 103-67-3, N-Methylbenzylamine 110-02-1, Thiophene 141-84-4, Rhodanine
 349-76-8 394-50-3, 3-Fluoro-2-hydroxybenzaldehyde 403-42-9 450-95-3,
 2-Fluoroacetophenone 452-08-4, 2-Bromo-4-fluoroanisole 459-60-9,
 4-Fluoroanisole 585-74-0 586-37-8 625-36-5, 3-Chloropropionyl
 chloride 673-22-3, 2-Hydroxy-4-methoxybenzaldehyde 709-63-7,
 4-(Trifluoromethyl)acetophenone 758-16-7, N,N-Dimethylthioformamide
 1423-61-6, 7-Bromobenzothiophene 2032-35-1, Bromoacetaldehyde diethyl
 acetal 2365-48-2, Methyl thioglycolate 7168-85-6, 7-Methoxy-1-
 benzofuran 7217-59-6, 2-Methoxybenzenethiol 7507-86-0,
 2-Bromo-5-methoxybenzaldehyde 13414-95-4, 6,7-Dihydrobenzothiophen-4(5H)-
 one 18776-12-0, 3-Chloro-1-phenylpropan-1-ol 19301-35-0,
 Benzothiophen-5-ol 19301-39-4, Benzothiophen-6-ol 19415-51-1,
 5-Fluoro-2-methoxybenzaldehyde 22069-06-3, Benzothiophene-4-thiol
 24070-51-7 88791-12-2, 4-Bromo-7-methoxybenzothiophene 100306-33-0,
 (R)-(+)-3-Chloro-1-phenyl-1-propanol 100306-34-1, (S)-(-)-3-Chloro-1-
 phenyl-1-propanol 105728-90-3, 2-Fluoro-5-methoxybenzaldehyde
 115144-40-6, 3,4-Difluoroanisole 147460-41-1, 2-Bromo-5-fluorophenol
 324769-10-0, 7-Bromo-6-fluorobenzothiophene 476199-14-1,
 4-Methoxybenzothiophene-2-carboxylic acid

RL: RCT (Reactant); RACT (Reactant or reagent)

(preparation of (benzothienyloxy)propanamine **serotonin** and **norepinephrine reuptake inhibitors** from thiophenols, phenylthioacetones, phenylmercaptopropenoic acids, or benzothiophenols)

IT 480-97-7, Benzofuran-4-ol 2439-68-1, 5-Benzyloxy-1-methyl-1H-indole
20289-27-4, 7-Benzyloxy-1H-indole 476199-33-4, 7-Benzyloxymethyl-1H-indole

RL: RCT (Reactant); RACT (Reactant or reagent)

(preparation of (heteroaryloxy)propanamine **serotonin** and **norepinephrine reuptake inhibitors** for treatment of **depression**, urinary incontinence, **pain**, and other CNS disorders)

IT 476199-94-7P, (3S)-3-[(Benzothien-7-yl)oxy]-N-methyl-3-phenyl-1-propanamine oxalate (1:1) 476199-96-9P, (3S)-3-[(Benzothien-4-yl)oxy]-N-methyl-3-phenyl-1-propanamine oxalate (1:1) 476199-98-1P, (3S)-3-[(Benzothien-5-yl)oxy]-N-methyl-3-phenyl-1-propanamine oxalate (1:1) 476199-99-2P, (3S)-3-[(Benzothien-6-yl)oxy]-N-methyl-3-phenyl-1-propanamine hydrochloride 476200-05-2P, (3S)-3-[(4-Fluorobenzothien-7-yl)oxy]-N-methyl-3-phenyl-1-propanamine oxalate (1:1) 476200-06-3P, (3S)-3-[(4-Fluoro-3-methylbenzothien-7-yl)oxy]-N-methyl-3-phenyl-1-propanamine hydrochloride 476200-07-4P, (3S)-3-[(3-Chloro-4-fluorobenzothien-7-yl)oxy]-N-methyl-3-phenyl-1-propanamine hydrochloride 476200-08-5P, (3S)-3-[(4-Methylbenzothien-7-yl)oxy]-N-methyl-3-phenyl-1-propanamine hydrochloride 476200-09-6P, (3S)-3-[(2-Fluorobenzothien-7-yl)oxy]-N-methyl-3-phenyl-1-propanamine hydrochloride 476200-10-9P, (3S)-3-[(2-Fluorobenzothien-4-yl)oxy]-N-methyl-3-phenyl-1-propanamine hydrochloride 476200-11-0P, (3S)-3-[(5-Fluorobenzothien-7-yl)oxy]-N-methyl-3-phenyl-1-propanamine hydrochloride 476200-12-1P, (3S)-3-[(4-Trifluoromethylbenzothien-6-yl)oxy]-N-methyl-3-phenyl-1-propanamine hydrochloride 476200-13-2P, (3S)-3-[(5-Fluorobenzothien-4-yl)oxy]-N-methyl-3-phenyl-1-propanamine hydrochloride 476200-14-3P, (3S)-3-[(7-Fluorobenzothien-4-yl)oxy]-N-methyl-3-phenyl-1-propanamine hydrochloride 476200-15-4P, (3S)-3-[(7-Fluoro-3-methylbenzothien-4-yl)oxy]-N-methyl-3-phenyl-1-propanamine hydrochloride 476200-16-5P, (3S)-3-[(4-Cyanobenzothien-7-yl)oxy]-N-methyl-3-phenyl-1-propanamine hydrochloride 476200-18-7P, (3S)-3-[(2-Cyanobenzothien-7-yl)oxy]-N-methyl-3-phenyl-1-propanamine fumarate (1:1) 476200-20-1P, (3S)-3-[(2-Cyanobenzothien-4-yl)oxy]-N-methyl-3-phenyl-1-propanamine fumarate (1:1) 476200-21-2P, (3S)-3-[(4-Fluoro-2-cyanobenzothien-7-yl)oxy]-N-methyl-3-phenyl-1-propanamine 476200-23-4P, (3S)-3-[(2-Cyanobenzothien-6-yl)oxy]-N-methyl-3-phenyl-1-propanamine difumarate 476200-24-5P, (3S)-3-[(6-Fluorobenzothien-7-yl)oxy]-N-methyl-3-phenyl-1-propanamine hydrochloride 476200-28-9P, (3S)-3-[(Benzothien-7-yl)oxy]-3-phenyl-1-propanamine oxalate (1:1) 476200-30-3P, (3S)-3-[(4-Fluorobenzothien-7-yl)oxy]-3-phenyl-1-propanamine oxalate (1:1) 476200-32-5P, (3S)-3-[(Benzothien-7-yl)oxy]-N-methyl-3-(2-thienyl)-1-propanamine oxalate (1:1) 476200-34-7P, (3R)-3-[(Benzothien-7-yl)oxy]-N-methyl-3-phenyl-1-propanamine oxalate (1:1) 476200-36-9P, (3R)-3-[(Benzothien-4-yl)oxy]-N-methyl-3-phenyl-1-propanamine oxalate (1:1) 476200-38-1P, (3R)-3-[(Benzothien-5-yl)oxy]-N-methyl-3-phenyl-1-propanamine oxalate (1:1) 476200-39-2P, (3R)-3-[(Benzothien-6-yl)oxy]-N-methyl-3-phenyl-1-propanamine hydrochloride 476200-45-0P, (3R)-3-[(4-Fluorobenzothien-7-yl)oxy]-N-methyl-3-phenyl-1-propanamine oxalate (1:1) 476200-46-1P, (3R)-3-[(4-Fluoro-3-methylbenzothien-7-yl)oxy]-N-methyl-3-phenyl-1-propanamine hydrochloride 476200-47-2P, (3R)-3-[(3-Chloro-4-fluorobenzothien-7-yl)oxy]-N-methyl-3-phenyl-1-propanamine hydrochloride 476200-48-3P, (3R)-3-[(4-Methylbenzothien-7-yl)oxy]-N-methyl-3-phenyl-1-propanamine hydrochloride 476200-49-4P, (3R)-3-[(2-Fluorobenzothien-7-yl)oxy]-N-methyl-3-phenyl-1-propanamine

hydrochloride 476200-50-7P, (3R)-3-[(2-Fluorobenzothien-4-yl)oxy]-N-methyl-3-phenyl-1-propanamine hydrochloride 476200-51-8P, (3R)-3-[(5-Fluorobenzothien-7-yl)oxy]-N-methyl-3-phenyl-1-propanamine hydrochloride 476200-52-9P, (3R)-3-[(4-Trifluoromethylbenzothien-6-yl)oxy]-N-methyl-3-phenyl-1-propanamine hydrochloride 476200-53-0P, (3R)-3-[(5-Fluorobenzothien-4-yl)oxy]-N-methyl-3-phenyl-1-propanamine hydrochloride 476200-54-1P, (3R)-3-[(7-Fluorobenzothien-4-yl)oxy]-N-methyl-3-phenyl-1-propanamine hydrochloride 476200-55-2P, (3R)-3-[(7-Fluoro-3-methylbenzothien-4-yl)oxy]-N-methyl-3-phenylpropanamine hydrochloride 476200-56-3P, (3R)-3-[(4-Cyanobenzothien-7-yl)oxy]-N-methyl-3-phenyl-1-propanamine hydrochloride 476200-58-5P, (3R)-3-[(2-Cyanobenzothien-7-yl)oxy]-N-methyl-3-phenyl-1-propanamine fumarate (1:1) 476200-60-9P, (3R)-3-[(2-Cyanobenzothien-4-yl)oxy]-N-methyl-3-phenyl-1-propanamine fumarate (1:1) 476200-62-1P, (3R)-3-[(2-Cyano-4-fluorobenzothien-7-yl)oxy]-N-methyl-3-phenyl-1-propanamine fumarate (1:1) 476200-64-3P, (3R)-3-[(2-Cyanobenzothien-6-yl)oxy]-N-methyl-3-phenyl-1-propanamine difumarate 476200-65-4P, (3R)-3-[(6-Fluorobenzothien-7-yl)oxy]-N-methyl-3-phenyl-1-propanamine hydrochloride 476200-75-6P, (3R)-3-[(Benzothien-7-yl)oxy]-3-phenyl-1-propanamine oxalate (1:1) 476200-77-8P, (3R)-3-[(4-Fluorobenzothien-7-yl)oxy]-3-phenyl-1-propanamine oxalate (1:1) 476200-78-9P, 3-[(Benzothien-7-yl)oxy]-N-methyl-3-(4-fluorophenyl)-1-propanamine 476200-79-0P, 3-[(Benzothien-7-yl)oxy]-N-methyl-3-(3-methylphenyl)-1-propanamine 476200-80-3P, 3-[(Benzothien-7-yl)oxy]-N-methyl-3-(2-fluorophenyl)-1-propanamine 476200-81-4P, 3-[(Benzothien-7-yl)oxy]-N-methyl-3-(3-fluorophenyl)-1-propanamine 476200-82-5P, 3-[(Benzothien-7-yl)oxy]-N-methyl-3-(3-methoxyphenyl)-1-propanamine 476200-83-6P, 3-[(Benzothien-7-yl)oxy]-N-methyl-3-(3-trifluoromethylphenyl)-1-propanamine 476200-84-7P, 3-[(Benzothien-7-yl)oxy]-N-methyl-3-(4-trifluoromethylphenyl)-1-propanamine 476200-85-8P, (3S)-3-[(Benzothienyl-7-yl)thio]-N-methyl-3-phenyl-1-propanamine 476200-86-9P, (3R)-3-[(Benzothienyl-7-yl)thio]-N-methyl-3-phenyl-1-propanamine 476200-87-0P, (3S)-3-[(Benzothienyl-4-yl)thio]-N-methyl-3-phenyl-1-propanamine hydrochloride 476200-88-1P, (3R)-3-[(Benzothienyl-4-yl)thio]-N-methyl-3-phenyl-1-propanamine hydrochloride

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(serotonin and norepinephrine reuptake

inhibitor; preparation of (benzothienyloxy)propanamine

serotonin and norepinephrine reuptake

inhibitors from thiophenols, phenylthioacetones,

phenylmercaptopropenoic acids, or benzothiophenols)

IT 476200-01-8P, (3S)-3-[(1H-Indol-7-yl)oxy]-N-methyl-3-phenyl-1-propanamine oxalate (1:1) 476200-03-0P, (3S)-3-[(1H-Indol-4-yl)oxy]-N-methyl-3-phenyl-1-propanamine oxalate (1:1) 476200-25-6P, N-Methyl-[(3S)-[(1-methyl-1H-indol-5-yl)oxy]-3-phenylpropyl]amine hydrochloride 476200-26-7P, N-Methyl-[(3S)-[(1-methyl-1H-indol-7-yl)oxy]-3-phenylpropyl]amine hydrochloride 476200-41-6P, (3R)-3-[(1H-Indol-7-yl)oxy]-N-methyl-3-phenyl-1-propanamine oxalate (1:1) 476200-43-8P, (3R)-3-[(1H-Indol-4-yl)oxy]-N-methyl-3-phenyl-1-propanamine oxalate (1:1) 476200-66-5P, N-Methyl-[(3R)-[(1-methyl-1H-indol-5-yl)oxy]-3-phenylpropyl]amine hydrochloride 476200-67-6P, [(3R)-[(Benzofuran-4-yl)oxy]-3-phenylpropyl]methanamine hydrochloride 476200-70-1P, [(3S)-[(Benzofuran-4-yl)oxy]-3-phenylpropyl]methanamine hydrochloride 476200-71-2P, [(3S)-[(Benzofuran-7-yl)oxy]-3-phenylpropyl]methanamine hydrochloride 476200-73-4P, [(3R)-[(Benzofuran-7-yl)oxy]-3-phenylpropyl]methanamine hydrochloride

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(**serotonin and norepinephrine reuptake inhibitor**; preparation of (heteroaryloxy)propanamine **serotonin and norepinephrine reuptake inhibitors** for treatment of **depression**, urinary incontinence, **pain**, and other CNS disorders)

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 114 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 30

ACCESSION NUMBER: 2002:395252 HCAPLUS

DOCUMENT NUMBER: 137:27684

TITLE: The role of **antidepressants** in the treatment of chronic **pain**

AUTHOR(S): Kakuyama, Masahiro; Fukuda, Kazuhiko

CORPORATE SOURCE: Department of Anesthesia, Kyoto University Hospital, Kyoto, 606-8507, Japan

SOURCE: Pain Reviews (2000), 7(3/4), 119-128

CODEN: PAREFV; ISSN: 0968-1302

PUBLISHER: Arnold, Hodder Headline

DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

AB A review. The efficacy of tricyclic and tetracyclic **antidepressants** in chronic **pain**, including postherpetic neuralgia, **painful** diabetic neuropathy, cancer **pain**, headache and fibromyalgia, have been assessed in many randomized controlled studies. Currently, tricyclic **antidepressants** are the first line treatment for chronic **pain** such as postherpetic neuralgia and painful diabetic neuropathy; they are also effective for migraine and chronic tension-type headache, in spite of their unwanted side-effects. Some new antidepressants such as selective serotonin (5-HT) reuptake inhibitors, 5-HT₂ antagonists and reversible monoamine oxidase-A inhibitors have been also assessed, but their efficacy in chronic pain has not been established. Other new antidepressants, such as selective **serotonin-norepinephrine reuptake inhibitors** and selective noradrenergic **reuptake inhibitors**, are also expected to be useful in chronic pain, but they have not so far been fully assessed.

CC 1-0 (Pharmacology)

ST review **antidepressant** chronic **pain**

IT **Pain**

(chronic; role of **antidepressants** in treatment of chronic **pain**)

IT Human

(role of **antidepressants** in treatment of chronic **pain**)

REFERENCE COUNT: 60 THERE ARE 60 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 115 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 31

ACCESSION NUMBER: 1995:970985 HCAPLUS

DOCUMENT NUMBER: 124:44542

TITLE: New antidepressant agents: Recent pharmacological developments leading to improved efficacy

AUTHOR(S): Goodnick, Paul J.; Benitez, Amparo

CORPORATE SOURCE: School Medicine, University Miami, Miami, FL, 33136, USA

SOURCE: Expert Opinion on Investigational Drugs (1995), 4(10),
935-43
CODEN: EOIDER; ISSN: 0967-8298
PUBLISHER: Ashley Publications
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review with 42 refs. The disadvantages of the standard tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs), in terms of side-effects and fatal overdose, led to the development and release of seven new antidepressants in the USA in the past eight years with approx. another ten in various stages of development. This paper will focus on how recent advances in biochem. and kinetics have led to improved efficacy. In particular, the more specific 5-HT agents appear effective for "typical" **depression** and **pain**; the less specific ones for **depression** associated with obsessive-compulsive disorder. The selective serotonin reuptake inhibitors (SSRIs) are particularly suited for treatment of depression associated with diabetes mellitus; the **serotonin and norepinephrine reuptake inhibitor** (SNRI), venlafaxine, for resistant depression; and bupropion, for atypical depression. The serotonin receptor modulator (SRM), nefazodone, in contrast, is particularly suited for the treatment of depression associated with insomnia because of its combined SSRI and post-synaptic 5-HT_{2A/C} receptor antagonist effects. In terms of kinetics, important factors include, particularly: elimination half-lives, linearity of kinetics, therapeutic blood levels, effects on hepatic microenzymes, and effects on memory and alertness. Discussion of these seven antidepressants is followed by a brief review of knowledge concerning other potential antidepressants in development.

CC 1-0 (Pharmacology)

L91 ANSWER 116 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2005:673104 HCAPLUS

DOCUMENT NUMBER: 143:146710

TITLE: Weak to average strength opioids or their combinations containing antidepressants for the treatment of depressions and anxiety disorders

INVENTOR(S): Bloms-Funke, Petra; Tzschentke, Thomas

PATENT ASSIGNEE(S): Gruenenthal G.m.b.H., Germany

SOURCE: PCT Int. Appl., 24 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: German

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005067916	A1	20050728	WO 2005-EP255	20050113
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW			
RW:	BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG			

DE 102004011392 A1 20050804 DE 2004-102004011392 20040305
PRIORITY APPLN. INFO.: DE 2004-102004001968A 20040113
DE 2004-102004011392A 20040305

AB The invention relates to weak to average strength opioids or combinations of said opioids containing antidepressants for the treatment of depressions and anxiety disorders, in addition to a method for treating depressions and anxiety disorders. The following combinations were tested on rats in the elevated plus maze test: tilidine with nisoxetine, tilidine with venflaxine and pethidin with nisoxetine.

IC ICM A61K031-343

ICS A61K031-137; A61K031-216; A61K031-452; A61P025-24

CC 1-11 (Pharmacology)

Section cross-reference(s): 63

IT **Mental disorder**

(depression; weak to average strength opioids or their combinations containing antidepressants for treatment of depressions and anxiety disorders)

IT 50-47-5, Desipramine 50-48-6, Amitriptyline 50-49-7, Imipramine
57-42-1, Pethidin 113-53-1, Dothiepin 303-49-1, Clomipramine
359-83-1, Pentazocin 438-60-8, Protriptyline 469-62-5,
Dextropropoxyphene 739-71-9, Trimipramine 1668-19-5, Doxepine
10262-69-8, Maprotiline 14028-44-5, Amoxapine 15574-96-6, Pizotyline
19794-93-5, Trazodon 20594-83-6, Nalbuphine 23047-25-8, Lofepramine
24219-97-4, Mianserine 24526-64-5, Nomifensin 24701-51-7,
Demexiptiline 25905-77-5, Minaprine 26629-87-8, Oxaflozane
31721-17-2, Quinupramine 32359-34-5, Medifoxamine 34911-55-2,
Bupropion 46817-91-8, Viloxazin 51931-66-9, Tilidine 53179-07-0,
Nisoxetine 54188-38-4, Metralindole 54340-58-8, Meptazinol
54739-18-3, Fluvoxamine 54910-89-3, Fluoxetine 56775-88-3, Zimeldine
57262-94-9, Teciptilline 57574-09-1, Amineptine 59729-33-8, Citalopram
60324-59-6, Nomelidine 61869-08-7, Paroxetine 71620-89-8, Reboxetine
72797-41-2, Tianeptine 79617-96-2, Sertraline 83015-26-3, Tomoxetine
83366-66-9, Nefazodone 85650-52-8, Mirtazapine 92623-85-3,
Milnacipran 93413-69-5, Venlafaxine 106650-56-0,
Sibutramine 116539-59-4, Duloxetine 128196-01-0, Escitalopram
163521-12-8, Vilazodone 860268-58-2 860268-60-6 860268-63-9

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(weak to average strength opioids or their combinations containing antidepressants for treatment of depressions and anxiety disorders)

REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 117 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2005:588665 HCAPLUS

DOCUMENT NUMBER: 143:103256

TITLE: Combination of a sedative and a neurotransmitter modulator for improving sleep quality and treating depression

INVENTOR(S): Lalji, Karim; Barberich, Timothy J.; Caron, Judy; Wessel, Thomas

PATENT ASSIGNEE(S): Sepracor Inc., USA

SOURCE: PCT Int. Appl., 394 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005060968	A1	20050707	WO 2004-US40962	20041208
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2005176680	A1	20050811	US 2004-7795	20041208
PRIORITY APPLN. INFO.:			US 2003-529156P	P 20031211
			US 2004-541614P	P 20040204
			US 2004-633213P	P 20041203
AB	One aspect of the present invention relates to pharmaceutical compns. containing 2 or more active agents that when taken together can be used to treat, e.g., insomnia and/or depression. The first component of the pharmaceutical composition is a GABA receptor modulating compound The second component of the pharmaceutical composition is a serotonin reuptake inhibitor (SRI), a norepinephrine reuptake inhibitor (NRI), a 5-HT2A modulator, or dopamine reuptake inhibitor (DRI). In certain embodiments, the pharmaceutical composition comprises eszopiclone. In a preferred embodiment, the pharmaceutical composition comprises eszopiclone and fluoxetine. The present invention also relates to a method of treating a sleep abnormality, treating insomnia, treating depression, augmenting antidepressant therapy, eliciting a dose-sparing effect, reducing depression relapse, improving the efficacy of antidepressant therapy or improving the tolerability of antidepressant therapy, comprising co-administering to a patient in need thereof a GABA-receptor-modulating compound; and a SRI, NRI, 5-HT2A modulator or DRI. Co-administration of eszopiclone with fluoxetine was well-tolerated and associated with rapid, sustained improvement in sleep and daytime symptoms in patients with MDD and insomnia. The rapid sleep improvement with adjunctive eszopiclone may be important, given the relatively slower onset of antidepressant effects with SSRIs.			
IC	ICM A61K031-4985			
	ICS A61K031-138; A61P025-20; A61P025-24			
CC	63-6 (Pharmaceuticals)			
	Section cross-reference(s): 1			
IT	Mental disorder (depression; combination of sedative and neurotransmitter modulator for improving sleep quality and treating depression)			
IT	50-47-5, Desipramine 110-89-4D, Piperidine, derivs. 303-49-1, Clomipramine 504-76-7D, Oxazolidine, derivs. 10262-69-8, Maprotiline 23047-25-8, Lofepramine 31096-91-0D, Phenylindole, derivs. 34911-55-2, Bupropion 43200-80-2, Zopiclone 54739-18-3, Fluvoxamine 54910-89-3, Fluoxetine 56296-78-7, Fluoxetine hydrochloride 56433-44-4, Oxaprotiline 57574-09-1, Amineptine 59729-33-8, Citalopram 59859-58-4, Femoxetine 60719-82-6, Alaproclate 61869-08-7, Paroxetine 63758-79-2, Indalpine 64603-91-4 66208-11-5, Ifoxetine 71620-89-8, Reboxetine 76778-22-8, GBR-12935 79617-96-2, Sertraline 80410-36-2, Fezolamine 82626-48-0, Zolpidem 83015-26-3, Tomoxetine 92264-81-8 92623-85-3, Milnacipran 93413-62-8 93413-69-5,			

Venlafaxine 112922-55-1, Cericlamine 116539-59-4, Duloxetine
127625-29-0, Fananserine 128196-01-0, Escitalopram 130580-02-8, SR
46349B 139290-65-6, MDL 100907 142761-11-3 142761-12-4
146877-56-7, 2 β -Propanoyl-3 β -(4-tolyl)-tropane 151319-34-5,
Zaleplon 161178-10-5, YM 992 325715-02-4, Indiplon 856661-85-3

RL: PAC (Pharmacological activity); THU (Therapeutic
use); BIOL (Biological study); USES (Uses)

(combination of sedative and neurotransmitter modulator for improving
sleep quality and treating depression)

REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 118 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2005:517402 HCAPLUS

DOCUMENT NUMBER: 143:38422

TITLE: Combination therapy for dementia, depression and
apathy

INVENTOR(S): Sheldon, Leslie James

PATENT ASSIGNEE(S): Can.

SOURCE: PCT Int. Appl., 47 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005053703	A1	20050616	WO 2004-CA2071	20041202
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW			
RW:	BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG			

PRIORITY APPLN. INFO.: US 2003-526137P P 20031202

AB The invention provides compns. and kits for treating dementia, depression and apathy using combination therapy involving either a monoamine oxidase inhibitor or a selective serotonin reuptake inhibitor in combination with an anti-psychotic agent.

IC ICM A61K031-551

ICS A61K031-137; A61K031-5375; A61K031-519; A61P025-24; A61P025-28

CC 1-11 (Pharmacology)

IT **Mental disorder**

(apathy; combination therapy for dementia, depression and apathy)

IT **Mental disorder**

(dementia; combination therapy for dementia, depression and apathy)

IT **Mental disorder**

(depression; combination therapy for dementia, depression and apathy)

IT 51-12-7, Nialamide 51-71-8, Phenelzine 54-92-2, Iproniazid 55-52-7, Pheniprazine 59-63-2, Isocarboxazid 65-64-5, Mebanazine 67-45-8,

Furazolidone 155-09-9, Tranylcypromine 156-51-4, Phenelzine sulfate 304-21-2, Harmaline 305-33-9, Iproniazid phosphate 306-19-4, Pivalylbenzhydrazine 442-51-3, Harmine 548-04-9, Hypericin 555-57-7, Pargyline 2235-90-7, Etryptamine 3544-35-2, Iproclozide 3818-37-9, Phenoxypipazine 4684-87-1, Octamoxin 5388-85-2, L 51641 5786-21-0, Clozapine 7654-03-7, Benmoxin 13492-01-8, Tranylcypromine sulfate 14611-51-9, Selegiline 17780-72-2, Clorgyline 17780-75-5, Clorgyline hydrochloride 18381-60-7, L 54761 19271-25-1, L 54832 19794-93-5, Trazodone 26615-21-4, Zotepine 29218-27-7, Toloxatone 31314-38-2, Prodiptine 33419-68-0, Safrazine 52942-31-1, Etoferidone 54403-19-9, Sercloramine 54739-18-3, Fluvoxamine 54910-89-3, Fluoxetine 56296-78-7, Fluoxetine hydrochloride 59729-32-7, Citalopram hydrobromide 59729-33-8, Citalopram 59859-58-4, Femoxetine 60662-16-0, Binedaline 60929-23-9, Indeloxazine 61718-82-9, Fluvoxamine maleate 61869-08-7, Paroxetine 63638-91-5, Brofaromine 66208-11-5, Ifoxetine 71320-77-9, Moclobemide 73815-11-9, Cimoxatone 77518-07-1, Amiflamine 78246-49-8, Paroxetine hydrochloride 79559-97-0, Sertraline hydrochloride 79617-96-2, Sertraline 83366-66-9, Nefazodone 85278-68-8, MDL 72392 86408-33-5, LY 121768 90293-01-9, Bifemelane 91406-11-0, Esuprone 92623-85-3, Milnacipran 93413-62-8, Desvenlafaxine 93413-69-5, Venlafaxine 94011-82-2, Bazinaprine 99630-95-2, MDL 72394 105365-76-2, RS-8359 106516-24-9, Sertindole 111974-69-7, Quetiapine 128196-01-0, Escitalopram 132539-06-1, Olanzapine 134476-36-1, BW-1370U87 134564-82-2, Befloxatone 135204-83-0, T-794 146939-27-7, Ziprasidone 150366-18-0, E-2011

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(combination therapy for dementia, **depression** and apathy)

REFERENCE COUNT: 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 119 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2005:471926 HCAPLUS

DOCUMENT NUMBER: 143:26625

TITLE: Preparation of pyridines, pyrimidines, and pyrazolopyridazines as cyclooxygenase-2 inhibitors for the treatment of depressive disorders.

INVENTOR(S): Hagan, James Joseph; Ratti, Emiliangelo; Routledge, Carol

PATENT ASSIGNEE(S): Glaxo Group Limited, UK

SOURCE: PCT Int. Appl., 56 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005048999	A2	20050602	WO 2004-EP13070	20041117
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW			
RW:	BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LU, MC, NL, PL, PT, RO,			

SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR,
NE, SN, TD, TG

PRIORITY APPLN. INFO.:

GB 2003-26967 A 20031119
GB 2003-27937 A 20031202
GB 2004-1862 A 20040128

OTHER SOURCE(S):

MARPAT 143:26625

AB Use of title compds. e.g. [I; R1 = H, alkyl, fluoroalkyl, alkenyl, alkynyl, cycloalkylalkyl, bridged cycloalkyl, etc.; R2 = fluoroalkyl; R3 = alkyl, amino, carboxamide] for preparation of a medicament for treatment of depressive disorders is claimed. Thus, a mixture of 4-methylthioacetophenone and Me trifluoroacetate in MeOCMe₃ was treated over 30 min. with NaOMe in MeOH followed by heating at 40° for ≥3 h. AcOH and S-Me 2-thiopseudourea were added followed by concentration and heating at 110° overnight. AcOH was added and the mixture was cooled to 50° followed by addition of aqueous Na tungstate and then 30% H₂O₂ over 3 h. followed by heating at 50° for ≥12 h. The mixture was cooled to 20° and aqueous Na sulfite was added over ≥30 min. followed by aging for 1 h to give 90% 2-methylsulfonyl-4-[4-(methylsulfonyl)phenyl]-6-trifluoromethylpyrimidine. The latter was heated overnight with K₂CO₃ in MeOH at 50° to give 88.4% 2-butoxy-4-[4-(methylsulfonyl)phenyl]-6-trifluoromethylpyrimidine (II). In the chronic inescapable shock in rats model, II at 10 mg/kg orally with paroxetine 5 mg/kg orally gave a full reversal of the chronic escape deficit.

IC ICM A61K031-00

CC 28-16 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 1, 27, 63

IT **Mental disorder**

(depression, treatment; preparation of pyridines, pyrimidines, and pyrazolopyridazines as cyclooxygenase-2 inhibitors for the treatment of depressive disorders)

IT 50-47-5, Desipramine 50-48-6, Amitriptyline 50-49-7, Imipramine
72-69-5, Nortriptyline 113-53-1, Dothiepin 303-49-1, Clomipramine
739-71-9, Trimipramine 4317-14-0, Amitriptyline N-oxide 6829-98-7,
Imipramine N-oxide 13669-70-0, Nefopam 14028-44-5, Amoxapine
16398-39-3, Nitroxazepine 19794-93-5, Trazodone 29908-03-0,
Ademetionine 31721-17-2, Quinupramine 41717-30-0, Befuraline
42408-79-7, Pirandamine 54403-19-9, Sercloramine 54739-18-3,
Fluvoxamine 54739-19-4, Clovoxamine 54910-89-3, Fluoxetine
59729-33-8, Citalopram 59859-58-4, Femoxetine 59905-71-4, Org 6582
60719-82-6, Alaproclate 60762-57-4, Pirlindole 61869-08-7, Paroxetine
66208-11-5, Ifoxetine 66834-24-0, Cianopramine 67165-56-4,
Diclofensine 67384-24-1, Org 6997 72575-45-2, RU 25591 72714-74-0,
Vigualine 75991-50-3, Dazepinil 77372-73-7, 6-Nitroquipazine
79617-96-2, Sertraline 80410-36-2, Fezolamine 82852-08-2, CGP 6085
83366-66-9, Nefazodone 86811-09-8, Litoxetine 86939-10-8, Indatraline
89875-86-5, Tiflucarbine 89956-72-9, CL 255663 90667-30-4,
Cyanodothiepin 91524-14-0, Napamezole 92623-85-3, Milnacipran
93413-69-5, Venlafaxine 94011-82-2, Bazinaprine 96786-92-4,
McN 5707 96795-89-0, McN 5652 100568-03-4, R-Fluoxetine
106650-56-0, Sibutramine 110763-25-2, WY 27587 112192-04-8,
Roxindole 112922-55-1, Cericlamine 116539-59-4, Duloxetine
119356-77-3, Dapoxetine 126924-38-7, Seproxetine 128196-01-0,
Escitalopram 145969-30-8, OPC 14523 163521-12-8, EMD 68843
191286-75-6, LY 214281 219907-10-5, VN 2222 242473-60-5, S 33005
257863-96-0, NS 2389

RL: **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)

(coadministration; preparation of pyridines, pyrimidines, and
pyrazolopyridazines as cyclooxygenase-2 inhibitors for the treatment of

depressive disorders)

L91 ANSWER 120 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN
 ACCESSION NUMBER: 2005:409332 HCAPLUS
 DOCUMENT NUMBER: 142:435753
 TITLE: Use of prickly pear (opuntia) plant parts and/or
 extracts for the treatment of depressions
 INVENTOR(S): Noeldner, Michael; Schoetz, Karl
 PATENT ASSIGNEE(S): Bioplanta Arzneimittel GmbH, Germany
 SOURCE: PCT Int. Appl., 20 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: German
 FAMILY ACC. NUM. COUNT: 2
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
-----	----	-----	-----	-----
WO 2005041994	A1	20050512	WO 2004-EP12070	20041026
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				

DE 10350194 A1 20050616 DE 2003-10350194 20031028

PRIORITY APPLN. INFO.: DE 2003-10350194 A 20031028

AB The invention relates to the use of opuntia, plant parts thereof, and/or
 exts. or other preps. produced therefrom for the treatment of depressive
 moods and diseases or other affective disorders which can be influenced by
 antidepressants, such as anxiety and panic disorders, bipolar depressions,
 somatization disorders, premenstrual syndrome, and precursors of such
 diseases. Thus 200g dry, finely ground Opuntia ficus Indica flowers were
 extracted twice with 1400 g 60% ethanol at 60°C. The extract was
 filtered; ethanol was evaporated in vacuum; the aqueous residue was freeze
 dried;
 the product was dried in vacuum over phosphorus pentoxide to obtain 30.2 g
 dry extract A tablet included (mg): dry extract of Opuntia ficus Indica 100.0;
 cellulose 117.0; lactose monohydrate 58.0; croscarmellose 15.0; silica
 3.0; magnesium stearate 6.0; hydroxypropylmethylcellulose 15.0;
 polyethylene glycol 3.0; talc 1.0; titanium dioxide 2.0.

IC ICM A61K035-78

ICS A61K031-135; A61P025-24

CC 63-4 (Pharmaceuticals)

Section cross-reference(s): 1

IT **Mental disorder**

(depression; use of prickly pear (opuntia) plant parts and/or
 exts. for treatment of depressions)

IT 93413-69-5, Venlafaxine

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(combination with; use of prickly pear (opuntia) plant parts and/or
 exts. for treatment of depressions)

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS
 RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 121 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN
 ACCESSION NUMBER: 2005:395500 HCAPLUS
 DOCUMENT NUMBER: 142:442858
 TITLE: Inversion on chromosome 8p23 is a risk factor for anxiety disorders, depression and bipolar
 INVENTOR(S): Bjornsdottir, Soley; Kong, Augustine; Thorgeirsson, Thorgeir E.
 PATENT ASSIGNEE(S): Decode Genetics Ehf., Iceland
 SOURCE: PCT Int. Appl., 200 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005040427	A2	20050506	WO 2004-US30699	20040917
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				

PRIORITY APPLN. INFO.: US 2003-504307P P 20030919
 AB An association between psychiatric disorders and disorders comorbid with psychiatric disorders, and genetic markers in the 8p23 genomic region is described. Markers are also provided to diagnose or detect a susceptibility to disorders comorbid with panic disorder and independently of comorbidity with panic disorder. Methods and surrogate markers for detecting the orientation of the Inv8p23 inversion fragment, thereby diagnosing psychiatric disorders or comorbid disorders or a susceptibility to psychiatric disorders or comorbid disorders, are also disclosed. The methods described herein are also useful for determining responsiveness of drugs

useful for treating psychiatric disorders.

IC ICM C12Q001-68

CC 3-1 (Biochemical Genetics)

Section cross-reference(s): 1, 14

IT **Mental disorder**

(Family denial; inversion on chromosome 8p23 is a risk factor for anxiety disorders, **depression** and bipolar)

IT **Mental disorder**

(bipolar disorder; inversion on chromosome 8p23 is a risk factor for anxiety disorders, **depression** and bipolar)

IT **Mental disorder**

(**depression**; inversion on chromosome 8p23 is a risk factor for anxiety disorders, **depression** and bipolar)

IT 5-HT reuptake inhibitors

Allele frequency

Blood analysis

DNA sequences

Drug screening

Genotypes
Haplotypes
Human

Hypercholesterolemia
Linkage disequilibrium

Mental disorder

Nervous system, disease
Susceptibility (genetic)

(inversion on chromosome 8p23 is a risk factor for anxiety disorders,
depression and bipolar)

IT **Mental disorder**

(obsession-compulsion; inversion on chromosome 8p23 is a risk factor
for anxiety disorders, **depression** and bipolar)

IT 54910-89-3, Fluoxetine 59729-32-7, Cipramil 59729-33-8, Citalopram
79617-96-2, Sertraline **93413-69-5**, Venlafaxine 128196-01-0,
Escitalopram 219861-08-2, Cipralex

RL: BUU (Biological use, unclassified); **THU (Therapeutic use)**;

BIOL (Biological study); USES (Uses)

(inversion on chromosome 8p23 is a risk factor for anxiety disorders,
depression and bipolar)

L91 ANSWER 122 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2005:232623 HCAPLUS

DOCUMENT NUMBER: 142:291420

TITLE: The combination of a serotonin reuptake inhibitor and
amoxapine for the treatment of depression and other
affective disorders

INVENTOR(S): Cremers, Thomas Ivo Franciscus Hubert; Willigers,
Sandra Hogg; Arnt, Jorn

PATENT ASSIGNEE(S): H. Lundbeck A/S, Den.

SOURCE: PCT Int. Appl., 26 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
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WO 2005023266	A1	20050317	WO 2004-DK580	20040901
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH,			
	CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD,			
	GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,			
	LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI,			
	NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY,			
	TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW			
RW:	BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM,			
	AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK,			
	EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE,			
	SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE,			
	SN, TD, TG			

PRIORITY APPLN. INFO.:

DK 2003-1269 A 20030904

US 2003-500792P P 20030904

AB The invention discloses the use of a combination of amoxapine and a
serotonin reuptake inhibitor (e.g. escitalopram), or any other compound,
which causes an elevation in the level of extracellular serotonin, for the
treatment of depression and other affective disorders.

IC ICM A61K031-553

ICS A61K031-343; A61P025-24; A61P025-22

CC 1-11 (Pharmacology)
IT **Mental disorder**
(affective; amoxapine-serotonin reuptake inhibitor combination for treatment of **depression** and other affective disorders)
IT **Mental disorder**
(attention deficit hyperactivity disorder; amoxapine-serotonin reuptake inhibitor combination for treatment of **depression** and other affective disorders)
IT **Mental disorder**
(cognitive; amoxapine-serotonin reuptake inhibitor combination for treatment of **depression** and other affective disorders)
IT **Mental disorder**
(**depression**; amoxapine-serotonin reuptake inhibitor combination for treatment of **depression** and other affective disorders)
IT **Mental disorder**
(neurotic **depression**; amoxapine-serotonin reuptake inhibitor combination for treatment of **depression** and other affective disorders)
IT **Mental disorder**
(obsession-compulsion; amoxapine-serotonin reuptake inhibitor combination for treatment of **depression** and other affective disorders)
IT **Mental disorder**
(phobia; amoxapine-serotonin reuptake inhibitor combination for treatment of **depression** and other affective disorders)
IT **Mental disorder**
(post-traumatic stress disorder; amoxapine-serotonin reuptake inhibitor combination for treatment of **depression** and other affective disorders)
IT **Mental disorder**
(psychosis; amoxapine-serotonin reuptake inhibitor combination for treatment of **depression** and other affective disorders)
IT **Mental disorder**
(schizoaffective disorder; amoxapine-serotonin reuptake inhibitor combination for treatment of **depression** and other affective disorders)
IT 50-49-7, Imipramine 303-49-1, Clomipramine 14028-44-5, Amoxapine 54739-18-3, Fluvoxamine 54910-89-3, Fluoxetine 59729-33-8, Citalopram 59859-58-4, Femoxetine 61869-08-7, Paroxetine 79617-96-2, Sertraline 83366-66-9, Nefazodone 93413-69-5, Venlafaxine 119356-77-3, Dapoxetine 128196-01-0, Escitalopram 823801-57-6 847739-83-7 847739-84-8 847739-85-9 847739-86-0 847739-87-1 847739-88-2 847739-89-3 847739-90-6 847739-91-7 847739-92-8 847739-93-9
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(amoxapine-serotonin reuptake inhibitor combination for treatment of **depression** and other affective disorders)

REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 123 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2005:232608 HCAPLUS

DOCUMENT NUMBER: 142:291419

TITLE: The combination of a serotonin reuptake inhibitor and loxapine for the treatment of depression and other affective disorders

INVENTOR(S): Cremers, Thomas Ivo Franciscus Hubert; Willigers, Sandra Hogg; Arnt, Jorn

PATENT ASSIGNEE(S) : H. Lundbeck A/S, Den.
 SOURCE: PCT Int. Appl., 27 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005023243	A1	20050317	WO 2004-DK581	20040901
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				

PRIORITY APPLN. INFO.: DK 2003-1270 A 20030904
 US 2003-500809P P 20030904

AB The invention discloses the use of a combination of loxapine and a serotonin reuptake inhibitor, e.g. escitalopram, for the treatment of depression and other affective disorders.

IC ICM A61K031-343
 ICS A61K031-553; A61P025-24; A61P025-22

CC 1-11 (Pharmacology)

IT **Mental disorder**
 (affective; loxapine-serotonin reuptake inhibitor combination for treatment of **depression** and other affective disorders)

IT **Mental disorder**
 (attention deficit hyperactivity disorder; loxapine-serotonin reuptake inhibitor combination for treatment of **depression** and other affective disorders)

IT **Mental disorder**
 (cognitive; loxapine-serotonin reuptake inhibitor combination for treatment of **depression** and other affective disorders)

IT **Mental disorder**
 (**depression**; loxapine-serotonin reuptake inhibitor combination for treatment of **depression** and other affective disorders)

IT **Mental disorder**
 (neurotic **depression**; loxapine-serotonin reuptake inhibitor combination for treatment of **depression** and other affective disorders)

IT **Mental disorder**
 (obsession-compulsion; loxapine-serotonin reuptake inhibitor combination for treatment of **depression** and other affective disorders)

IT **Mental disorder**
 (phobia; loxapine-serotonin reuptake inhibitor combination for treatment of **depression** and other affective disorders)

IT **Mental disorder**
 (post-traumatic stress disorder; loxapine-serotonin reuptake inhibitor combination for treatment of **depression** and other affective disorders)

IT **Mental disorder**
(psychosis; loxapine-serotonin reuptake inhibitor combination for treatment of **depression** and other affective disorders)

IT **Mental disorder**
(schizoaffective disorder; loxapine-serotonin reuptake inhibitor combination for treatment of **depression** and other affective disorders)

IT 50-49-7, Imipramine 303-49-1, Clomipramine 1977-10-2, Loxapine 54739-18-3, Fluvoxamine 54910-89-3, Fluoxetine 59729-33-8, Citalopram 59859-58-4, Femoxetine 61869-08-7, Paroxetine 79617-96-2, Sertraline 83366-66-9, Nefazodone 93413-69-5, Venlafaxine 119356-77-3, Dapoxetine 128196-01-0, Escitalopram 847829-23-6 847829-24-7 847829-25-8 847829-26-9 847829-27-0 847829-28-1 847829-29-2 847829-30-5 847829-31-6 847829-32-7 847829-33-8 847829-34-9
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(loxapine-serotonin reuptake inhibitor combination for treatment of **depression** and other affective disorders)

REFERENCE COUNT: 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 124 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2005:177917 HCAPLUS
DOCUMENT NUMBER: 142:274044
TITLE: The combination of a serotonin reuptake inhibitor and a glycine transporter type 1 (GlyT-1) inhibitor for the treatment of depression, anxiety, and other affective disorders
INVENTOR(S): Didriksen, Michael; Hogg Willigers, Sandra; Arnt, Jorn
PATENT ASSIGNEE(S): H. Lundbeck A/S, Den.
SOURCE: PCT Int. Appl., 39 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005018676	A1	20050303	WO 2004-DK547	20040818
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				

PRIORITY APPLN. INFO.: DK 2003-1198 A 20030821
US 2003-496738P P 20030821

AB The invention discloses the use of a compound which is a serotonin reuptake inhibitor and a compound, which is a GlyT-1 inhibitor for the preparation of a pharmaceutical composition for the treatment of depression, anxiety disorders, and other affective disorders. In particular the invention relates to treatment of depression, anxiety disorders, and other affective disorders, e.g. generalized anxiety disorder, panic anxiety, obsessive compulsive

disorder, acute stress disorder, post traumatic stress disorder and social anxiety disorder, eating disorders such as bulimia, anorexia and obesity, phobias, dysthymia, premenstrual syndrome, cognitive disorders, impulse control disorders, attention deficit hyperactivity disorder, drug abuse or any other disorder responsive to serotonin reuptake inhibitors. The invention also discloses a pharmaceutical composition comprising a serotonin reuptake inhibitor and a GlyT-1 inhibitor.

- IC ICM A61K045-06
ICS A61P025-24
- CC 1-11 (Pharmacology)
Section cross-reference(s): 63
- IT **Mental disorder**
(affective; serotonin reuptake inhibitor-glycine transporter type 1 inhibitor combination for treatment of **depression**, anxiety, and other affective disorders)
- IT **Mental disorder**
(attention deficit hyperactivity disorder; serotonin reuptake inhibitor-glycine transporter type 1 inhibitor combination for treatment of **depression**, anxiety, and other affective disorders)
- IT **Mental disorder**
(cognitive; serotonin reuptake inhibitor-glycine transporter type 1 inhibitor combination for treatment of **depression**, anxiety, and other affective disorders)
- IT **Mental disorder**
(**depression**; serotonin reuptake inhibitor-glycine transporter type 1 inhibitor combination for treatment of **depression**, anxiety, and other affective disorders)
- IT **Mental disorder**
(impulse control disorder; serotonin reuptake inhibitor-glycine transporter type 1 inhibitor combination for treatment of **depression**, anxiety, and other affective disorders)
- IT **Mental disorder**
(neurotic **depression**; serotonin reuptake inhibitor-glycine transporter type 1 inhibitor combination for treatment of **depression**, anxiety, and other affective disorders)
- IT **Mental disorder**
(obsession-compulsion; serotonin reuptake inhibitor-glycine transporter type 1 inhibitor combination for treatment of **depression**, anxiety, and other affective disorders)
- IT **Mental disorder**
(phobia; serotonin reuptake inhibitor-glycine transporter type 1 inhibitor combination for treatment of **depression**, anxiety, and other affective disorders)
- IT **Mental disorder**
(post-traumatic stress disorder; serotonin reuptake inhibitor-glycine transporter type 1 inhibitor combination for treatment of **depression**, anxiety, and other affective disorders)
- IT 50-49-7, Imipramine 303-49-1, Clomipramine 54739-18-3, Fluvoxamine 54910-89-3, Fluoxetine 59729-32-7, Citalopram hydrobromide 59729-33-8, Citalopram 59859-58-4, Femoxetine 61869-08-7, Paroxetine 79617-96-2, Sertraline 83366-66-9, Nefazodone 93413-69-5, Venlafaxine 116539-59-4, Duloxetine 119356-77-3, Dapoxetine 128196-01-0, Escitalopram 163521-12-8, Vilazodone 392286-28-1 392286-29-2 392286-56-5 392286-57-6 392286-58-7 392286-60-1 392286-62-3 392286-63-4 392286-64-5 392286-65-6 392286-66-7 392286-67-8 392286-68-9 392286-69-0 392286-70-3 392286-71-4 392286-72-5 392286-74-7 392286-75-8 392286-76-9 392286-77-0 392286-78-1 392286-79-2 392286-80-5 405225-21-0, Lu 2736N 556113-55-4

556113-56-5	556113-57-6	556113-58-7	556113-59-8	556113-60-1
556113-61-2	556113-62-3	556113-63-4	556113-64-5	556113-65-6
556113-66-7	556113-67-8	556113-69-0	556113-70-3	556113-71-4
556113-72-5	556113-73-6	632366-88-2	685503-51-9	700802-91-1
710277-49-9	715653-54-6	726124-62-5	730934-49-3	736128-71-5
742688-76-2	743413-15-2	744190-72-5	745031-43-0	748124-77-8
749200-58-6	751473-17-3	767279-54-9	770701-69-4	772331-56-3
780030-51-5	780746-34-1	788814-56-2	791578-53-5	847030-24-4
847030-25-5	847030-26-6	847030-27-7	847030-28-8	847030-29-9
847030-30-2	847030-31-3	847030-32-4	847030-33-5	847030-34-6
847030-35-7	847030-37-9	847030-38-0	847030-39-1	847030-40-4
847030-41-5	847030-42-6	847030-43-7	847030-44-8	847030-45-9
847030-46-0	847030-47-1	847030-48-2		

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(serotonin reuptake inhibitor-glycine transporter type 1 inhibitor combination for treatment of depression, anxiety, and other affective disorders)

REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 125 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2005:29189 HCAPLUS

DOCUMENT NUMBER: 142:127610

TITLE: The combination of a serotonin reuptake inhibitors and agomelatine for the treatment of depression and other affective disorders

INVENTOR(S): Willigers, Sandra

PATENT ASSIGNEE(S): H. Lundbeck A/S, Den.

SOURCE: PCT Int. Appl., 22 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
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WO 2005002562	A1	20050113	WO 2004-DK464	20040629
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW			
RW:	BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG			

PRIORITY APPLN. INFO.: DK 2003-1031 A 20030704
US 2003-485479P P 20030707

AB The invention discloses the use of a combination of agomelatine and a serotonin reuptake inhibitor (SRIs), or any other compound, which causes an elevation in the level of extracellular serotonin, for the treatment of depression and other affective disorders.

IC ICM A61K031-16

ICS A61K031-343; A61K031-138; A61K031-135; A61P025-24

CC 1-11 (Pharmacology)

IT **Mental disorder**
(affective; serotonin reuptake inhibitor-agomelatine combination for treatment of **depression** and other affective disorders)

IT **Mental disorder**
(attention deficit hyperactivity disorder; serotonin reuptake inhibitor-agomelatine combination for treatment of **depression** and other affective disorders)

IT **Mental disorder**
(cognitive; serotonin reuptake inhibitor-agomelatine combination for treatment of **depression** and other affective disorders)

IT **Mental disorder**
(**depression**; serotonin reuptake inhibitor-agomelatine combination for treatment of **depression** and other affective disorders)

IT **Mental disorder**
(impulse control disorder; serotonin reuptake inhibitor-agomelatine combination for treatment of **depression** and other affective disorders)

IT **Mental disorder**
(neurotic **depression**; serotonin reuptake inhibitor-agomelatine combination for treatment of **depression** and other affective disorders)

IT **Mental disorder**
(obsession-compulsion; serotonin reuptake inhibitor-agomelatine combination for treatment of **depression** and other affective disorders)

IT **Mental disorder**
(phobia; serotonin reuptake inhibitor-agomelatine combination for treatment of **depression** and other affective disorders)

IT **Mental disorder**
(post-traumatic stress disorder; serotonin reuptake inhibitor-agomelatine combination for treatment of **depression** and other affective disorders)

IT 50-49-7, Imipramine 303-49-1, Clomipramine 54739-18-3, Fluvoxamine 54910-89-3, Fluoxetine 59729-33-8, Citalopram 59859-58-4, Femoxetine 61869-08-7, Paroxetine 79617-96-2, Sertraline 83366-66-9, Nefazodone 93413-69-5, Venlafaxine 119356-77-3, Dapoxetine 128196-01-0, Escitalopram 138112-76-2, Agomelatine 824393-18-2 824393-20-6 824393-22-8 824393-23-9 824393-24-0 824393-25-1 824393-26-2 824393-27-3 824393-28-4 824393-29-5 824393-30-8 824393-31-9 824393-32-0
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(serotonin reuptake inhibitor-agomelatine combination for treatment of **depression** and other affective disorders)

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 126 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2005:1132922 HCAPLUS
TITLE: Use of gaboxadol for the treatment of depression and other affective disorders
INVENTOR(S): Sanchez, Connie; Ebert, Bjarke
PATENT ASSIGNEE(S): H. Lundbeck A/S, Den.
SOURCE: U.S. Pat. Appl. Publ., 9 pp., Cont.-in-part of Appl. No. PCT/DK04/000459.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English

FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2005234093	A1	20051020	US 2004-20632	20041222
WO 2004112786	A2	20041229	WO 2004-DK459	20040625
WO 2004112786	A3	20050414		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.:

US 2003-483019P	P	20030625
US 2004-535123P	P	20040107
WO 2004-DK459	A2	20040625
DK 2003-956	A	20030625
DK 2004-16	A	20040107

AB. The invention discloses the use of gaboxadol for preparing a pharmaceutical composition for treating depression. The invention also discloses the use of gaboxadol for the preparation of a pharmaceutical composition to be used in combination with a serotonin reuptake inhibitor, or any other compound which causes an elevation in the level of extracellular serotonin.

IC ICM A61K031-4745

INCL 514302000

CC 1-11 (Pharmacology)

Section cross-reference(s): 63

IT INDEXING IN PROGRESS

IT **Mental disorder**

(affective; gaboxadol for treatment of **depression** and other affective disorders, and combinations with serotonin reuptake inhibitors)

IT **Mental disorder**

(attention deficit hyperactivity disorder; gaboxadol for treatment of **depression** and other affective disorders, and combinations with serotonin reuptake inhibitors)

IT **Mental disorder**

(cognitive; gaboxadol for treatment of **depression** and other affective disorders, and combinations with serotonin reuptake inhibitors)

IT **Mental disorder**

(**depression**; gaboxadol for treatment of **depression** and other affective disorders, and combinations with serotonin reuptake inhibitors)

IT **Mental disorder**

(impulse control disorder; gaboxadol for treatment of **depression** and other affective disorders, and combinations with serotonin reuptake inhibitors)

IT **Mental disorder**

(neurotic **depression**; gaboxadol for treatment of **depression** and other affective disorders, and combinations with serotonin reuptake inhibitors)

IT **Mental disorder**

(phobia; gaboxadol for treatment of **depression** and other affective disorders, and combinations with serotonin reuptake inhibitors)

IT 50-49-7, Imipramine 303-49-1, Clomipramine 54739-18-3, Fluvoxamine 54910-89-3, Fluoxetine 59729-32-7, Citalopram hydrobromide 59729-33-8, Citalopram 59859-58-4, Femoxetine 61869-08-7, Paroxetine 64603-91-4, Gaboxadol 64603-91-4D, Gaboxadol, salts 79617-96-2, Sertraline 83366-66-9, Nefazodone 85118-33-8, Gaboxadol hydrochloride **93413-69-5**, Venlafaxine **116539-59-4**, Duloxetine 119356-77-3, Dapoxetine 128196-01-0, Escitalopram
 RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (gaboxadol for treatment of **depression** and other affective disorders, and combinations with serotonin reuptake inhibitors)

L91 ANSWER 127 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2005:1132659 HCAPLUS

TITLE: Lithium salt combinations with psychoactive drugs for the treatment of anxiety, depression or psychotic conditions

INVENTOR(S): Satow, Philip Maxwell

PATENT ASSIGNEE(S): USA

SOURCE: U.S. Pat. Appl. Publ., 21 pp.

CODEN: USXXCO

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2005233010	A1	20051020	US 2005-108476	20050418
WO 2005102366	A2	20051103	WO 2005-US13134	20050418
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				

PRIORITY APPLN. INFO.: US 2004-563347P P 20040419

AB The invention discloses combination therapies for treating anxiety, depression or psychotic conditions using a lithium salt and a psychoactive drug selected from a serotonin reuptake inhibitor, a 5HT2 receptor antagonist, an anticonvulsant, a norepinephrine reuptake inhibitor, an α -adrenoreceptor antagonist, an NK-3 antagonist, an NK-1 receptor antagonist, a PDE4 inhibitor, a neuropeptide Y5 Receptor antagonist, a D4 receptor antagonist, a 5HT1A receptor antagonist, a 5HT1D receptor antagonist, a CRF antagonist, a monoamine oxidase inhibitor, a sedative-hypnotic drug, and an atypical antipsychotic.

IC ICM A61K033-00

ICS A61K031-19

INCL 424715000; 514574000

CC 1-11 (Pharmacology)

IT INDEXING IN PROGRESS

IT **Mental disorder**
(bipolar disorder; lithium salt combination with psychoactive drug for treatment of anxiety, **depression** or psychotic conditions)

IT **Mental disorder**
(**depression**; lithium salt combination with psychoactive drug for treatment of anxiety, **depression** or psychotic conditions)

IT **Mental disorder**
(psychosis; lithium salt combination with psychoactive drug for treatment of anxiety, **depression** or psychotic conditions)

IT **Mental disorder**
(unipolar **depression**; lithium salt combination with psychoactive drug for treatment of anxiety, **depression** or psychotic conditions)

IT 50-06-6, Phenobarbital 50-47-5, Desipramine 50-48-6, Amitriptyline 50-49-7, Imipramine 51-12-7, Nialamide 51-71-8, Phenelzine 58-25-3, Chlordiazepoxide 59-63-2, Isocarboxazid 59-66-5, Acetazolamide 72-69-5, Nortriptyline 77-67-8, Ethosuximide 86-35-1, Ethotoin 99-66-1 108-01-0, Deanol 113-53-1, Dothiepin 115-38-8, Mephobarbital 125-33-7, Primidone 127-48-0, Trimethadione 155-09-9, Tranlycypromine 298-46-4, Carbamazepine 303-49-1, Clomipramine 438-60-8, Protriptyline 439-14-5, Diazepam 554-13-2, Lithium carbonate 604-75-1, Oxazepam 655-05-0, Thozalinone 739-71-9, Trimipramine 846-49-1, Lorazepam 919-16-4, Lithium citrate 1622-61-3, Clonazepam 1668-19-5, Doxepin 2955-38-6, Prazepam 3286-46-2, Sulbutiamine 4498-32-2, Dibenzepin 5560-72-5, Iprindole 5786-21-0, Clozapine 7439-93-2D, Lithium, salts 10262-69-8, Maprotiline 13669-70-0, Nefopam 14028-44-5, Amoxapine 14611-51-9, Selegiline 15301-93-6, Tofenacin 15574-96-6, Pizotiline 15676-16-1, Sulpiride 18464-39-6, Caroxazone 22316-47-8, Clobazam 22345-47-7, Tofisopam 23047-25-8, Lofepamine 23092-17-3, Halazepam 23651-95-8, Droxidopa 24219-97-4, Mianserin 24526-64-5, Nomifensine 24701-51-7, Demexiptiline 25451-15-4, Felbamate 25905-77-5, Minaprine 26629-87-8, Oxaflozane 28981-97-7, Alprazolam 29218-27-7, Toloxatone 29975-16-4, Estazolam 32359-34-5, Medifoxamine 34911-55-2, Bupropion 35764-73-9, Fluotracen 36505-84-7, Buspirone 37115-32-5, Adinazolam 41717-30-0, Befuraline 49763-96-4, Stiripentol 51022-73-2, Zometapine 52463-83-9, Pinazepam 52942-31-1, Etoperidone 53179-07-0, Nisoxetine 54188-38-4 54403-19-9 54739-18-3, Fluvoxamine 54739-19-4, Clovoxamine 56296-78-7, Prozac 56775-88-3, Zimelidine 57109-90-7, Chlorazepate 57262-94-9, Setiptiline 57574-09-1, Amineptine 59729-32-7, Celexa 59729-33-8, Citalopram 59859-58-4, Femoxetine 60142-96-3, Gabapentin 60662-16-0 60719-82-6, Alaproclate 60929-23-9, Indeloxazine 61718-82-9, Luvox 61869-08-7, Paroxetine 62305-86-6 62473-79-4, Teniloxazine 63638-91-5, Brofaromine 63758-79-2, Indalpine 66644-81-3, Veralipride 66834-24-0, Cianopramine 67765-04-2 68506-86-5, Vigabatrin 71320-77-9, Moclobemide 71620-89-8, Reboxetine 71827-56-0, Clemeprol 72714-74-0, Viqualine 72797-41-2, Tianeptine 73815-11-9, Cimoxatone 75991-50-3, Dazepinil 76496-68-9, Levoprotiline 78246-49-8 79467-22-4, Bipenamol 79559-97-0, Zolofit 79617-96-2, Sertraline 79944-58-4, Idazoxan 80018-06-0, Fengabine 80410-36-2 83015-26-3, Atomoxetine 83366-66-9, Nefazodone 83891-03-6, Norfluoxetine 83928-76-1, Gepirone 84057-84-1, Lamotrigine 85650-52-8, Mirtazapine 86811-09-8, Litoxetine 87051-43-2, Ritanserin 89875-86-5, Tiflucarbine 90243-66-6, Montirelin 90293-01-9, Bifemelane 92623-85-3, Milnacipran 93413-69-5, Venlafaxine 94011-82-2, Bazinaprine 95847-70-4, Ipsapirone 98159-82-1, Hydroxynefazodone 98206-10-1, Flesinoxan 104054-27-5, Atipamezole 106266-06-2, Risperidone 106516-24-9, Sertindole 106650-56-0, Sibutramine 111974-69-7, Quetiapine

112922-55-1, Cericlamine 116539-59-4, Duloxetine 117857-45-1,
 Loreclezole 132539-06-1, Olanzapine 146939-27-7, Ziprasidone
 153707-86-9 219861-08-2, Lexapro

RL: PAC (Pharmacological activity); THU (Therapeutic
 use); BIOL (Biological study); USES (Uses)

(lithium salt combination with psychoactive drug for treatment of
 anxiety, **depression** or psychotic conditions)

L91 ANSWER 128 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2005:1078241 HCAPLUS

DOCUMENT NUMBER: 143:367307

TITLE: Preparation of nitrogen-heterocycle-containing
 phenylaminopropanol derivatives and methods of their
 use to prevent and treat conditions ameliorated by
 monoamine reuptake

INVENTOR(S): Kim, Callain Younghee; Mahaney, Paige Erin; Trybulski,
 Eugene John; Zhang, Puwen; Terefenko, Eugene Anthony;
 Mccomas, Casey Cameron; Marella, Michael Anthony;
 Coghlan, Richard Dale; Heffernan, Gavin David; Cohn,
 Stephen Todd; Vu, An Thien; Sabatucci, Joseph Peter;
 Ye, Fei

PATENT ASSIGNEE(S): Wyeth, John, and Brother Ltd., USA

SOURCE: U.S. Pat. Appl. Publ., 115 pp.

CODEN: USXXCO

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2005222148	A1	20051006	US 2005-91885	20050328
WO 2005097744	A1	20051020	WO 2005-US10511	20050329
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW			
RW:	BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG			

PRIORITY APPLN. INFO.:

US 2004-557651P P 20040330

US 2004-569863P P 20040511

US 2005-91885 A 20050328

AB The present invention is directed to phenylaminopropanol derivs. (shown as I; variables defined below; e.g. (1RS,2SR)-1-(1H-indol-1-yl)-3-(4-methylpiperazin-1-yl)-1-phenylpropan-2-ol dihydrochloride (free base shown as II)) or pharmaceutically acceptable salts thereof, compns. containing these derivs., and methods of their use for the prevention and treatment of conditions ameliorated by monoamine reuptake including, inter alia, vasomotor symptoms (VMS), sexual dysfunction, gastrointestinal and genitourinary disorders, chronic fatigue syndrome, fibromyalgia syndrome, nervous system disorders, and combinations thereof, particularly those conditions major **depressive** disorder, vasomotor symptoms, stress and urge urinary incontinence, fibromyalgia, **pain**, diabetic neuropathy, and combinations thereof. Percent inhibitions of human

norepinephrine transporter by .apprx.200 examples of I are tabulated. For I: the dotted line between Y and Z = an optional double bond; Y is N, CR6, or C:O; Z is N, NR7, CR5, or C(R5)2; R1 = alkyl, alkoxy, halo, CF3, OCF3, arylalkyloxy substituted with 0-3 R11, aryloxy substituted with 0-3 R11, aryl substituted with 0-3 R11, heteroaryl substituted with 0-3 R11, hydroxy, alkanoyloxy, nitro, nitrile, alkenyl, alkynyl, alkyl sulfoxide, Ph sulfoxide substituted with 0-3 R11, alkyl sulfone, Ph sulfone substituted with 0-3 R11, alkylsulfonamide, phenylsulfonamide substituted with 0-3 R11, heteroaryloxy substituted with 0-3 R11, heteroarylmethoxy substituted with 0-3 R11, alkylamido, or arylamido substituted with 0-3 R11; or two adjacent R1 = methylenedioxy. R2 is aryl substituted with 0-3 R1 or heteroaryl substituted with 0-3 R1; R3 is H or C1-C4 alkyl; R4 = H, C1-C4 alkyl, arylalkyl, heteroarylmethyl, cycloheptylmethyl, cyclohexylmethyl, cyclopentylmethyl, or cyclobutylmethyl, or both R4 groups, together with the N through which they are attached, form a heterocyclic ring = 4-6 ring atoms, where one C may be optionally replaced with N, O, S, or SO2, and where any C ring atom or addnl. N atom may be (un)substituted with C1-C4 alkyl, F, or CF3; R5 = H, C1-C4 alkyl, aryl substituted with 0-3 R1, or cyano; or when two R5 are present, they form a carbocyclic ring = 3-7 carbons; R6 is H, C1-C4 alkyl, or cyano; R7 is H, C1-C6 alkyl, C3-C6 cycloalkyl, or aryl substituted with 0-3 R1; R8 is H, or C1-C4 alkyl; R9 is H, or C1-C4 alkyl; R10 = H, or C1-C4 alkyl; or R10 and R4 together with the N to which R4 is attached form a N-containing ring containing 3-6 C atoms; n = 0-4; x = 1, 2; and R11 is alkyl, alkoxy, halo, CF3, OCF3, hydroxy, alkanoyloxy, nitro, nitrile, alkenyl, alkynyl, alkyl sulfoxide, alkyl sulfone, alkylsulfonamide, or alkylamido; or two adjacent R11 = methylenedioxy; wherein 1-3 C atoms in ring A may optionally be replaced with N. Although the methods of preparation are not claimed, .apprx.200 example preps. are included. For example, II was prepared in 3 steps starting from indole and trans-3-phenylglycidol and involving intermediates (2RS,3RS)-3-(indol-1-yl)-3-phenylpropane-1,2-diol and (2RS,3RS)-toluene-4-sulfonic acid 2-hydroxy-3-(indol-1-yl)-3-phenylpropyl ester.

IC ICM A61K031-5377
ICS A61K031-496; A61K031-454; A61K031-4184; A61K031-416; C07D413-02;
C07D043-02
INCL 514232500; 514384000; 514406000; 514254060; 514320000; 514338000;
544139000; 544368000; 546199000; 548304100
CC 28-10 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 1, 25, 63
IT **Nervous system agents**
(noradrenaline reuptake inhibitors;
preparation of nitrogen-heterocycle-containing phenylaminopropanol derivs.
and
methods of use for conditions ameliorated by monoamine reuptake)

L91 ANSWER 129 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2005:904086 HCAPLUS
DOCUMENT NUMBER: 143:222548
TITLE: Novelty-induced hypophagia-based assays for
identifying agents to treat anxiety and depression
INVENTOR(S): Hen, Rene; Dulawa, Stephanie
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 20 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2005186137	A1	20050825	US 2004-977911	20041029

PRIORITY APPLN. INFO.: US 2003-516666P P 20031031

AB The invention provides a method for determining whether an agent reduces anxiety and/or depression in a depressed, non-human subject. The invention also provides methods for treating anxiety and depression in subjects afflicted with those disorders comprising administering a therapeutically effective amount of an anxiety-reducing or depression-reducing agent identified by the method. The methodol. of the invention uses a determination of rate of engagement in a pleasurable activity in a novel environment.

IC ICM A61K049-00

INCL 424009100

CC 1-11 (Pharmacology)

IT **Mental disorder**
(**depression**; novelty-induced hypophagia-based assays for identifying agents to treat anxiety and **depression**)

IT **Mental disorder**
(mood-affecting, lithium mood stabilizer; novelty-induced hypophagia-based assays for identifying agents to treat anxiety and **depression**)

IT 50-47-5, Desipramine 71620-89-8, Reboxetine 93413-69-5, Venlafaxine
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(novelty-induced hypophagia-based assays for identifying agents to treat anxiety and **depression**)

L91 ANSWER 130 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2005:824442 HCAPLUS

DOCUMENT NUMBER: 143:206461

TITLE: Limbic neurotransmission reduction-based method for the treatment of clinical depression

INVENTOR(S): Binder, Michael Raymond

PATENT ASSIGNEE(S): USA

SOURCE: U.S. Pat. Appl. Publ., 3 pp.
CODEN: USXXCO

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2005181071	A1	20050818	US 2005-58661	20050215

PRIORITY APPLN. INFO.: US 2004-545223P P 20040218
US 2004-581627P P 20040622

AB The invention is a new method for the treatment of clin. depression. The invention involves reducing neurotransmission in the limbic system of the human brain as a means of treating depressive symptoms.

IC ICM A61K031-5513
ICS A61K031-55; A61K031-195; A61K031-19

INCL 424722000; 514217000; 514221000; 514561000; 514557000; 514389000

CC 1-11 (Pharmacology)

IT **Mental disorder**
(**depression**; limbic neurotransmission reduction-based method for

treatment of clin. depression)

IT 50-52-2, Thioridazine 50-53-3, Thorazine, biological studies 52-86-8, Haldol 57-41-0, Phenytoin 58-38-8, Prochlorperazine 69-23-8, Fluphenazine 77-67-8 84-02-6, Compazine 99-66-1, Valproic acid 117-89-5, Trifluoperazine 125-33-7, Primidone 130-61-0, Mellaril 146-56-5, Prolixin 298-46-4, Tegretol 438-41-5, Librium 439-14-5, Valium 440-17-5, Stelazine 554-13-2, Eskalith 630-93-3, Dilantin 1069-66-5, Depakene 1622-61-3, Klonopin 2062-78-4, Orap 3313-26-6, Thiothixene 5588-33-0, Serentil 5591-45-7, Navane 5786-21-0, Clozaril 7416-34-4, Molindone 7439-93-2D, Lithium, salts 15622-65-8, Moban 28721-07-5 31677-93-7, Wellbutrin 34911-55-2, Bupropion 54739-18-3, Fluvoxamine 54910-89-3, Fluoxetine 56296-78-7, Prozac 59729-32-7, Celexa 59729-33-8, Citalopram 60142-96-3, Neurontin 61718-82-9, Luvox 61869-08-7, Paroxetine 68291-97-4, Zonisamide 76584-70-8, Depakote 78246-49-8 79559-97-0, Zoloft 79617-96-2, Sertraline 83366-66-9, Nefazodone 84057-84-1, Lamictal 85650-52-8, Remeron 93413-69-5, Venlafaxine 97240-79-4, Topamax 99300-78-4, Effexor 102767-28-2, Keppra 106266-06-2, Risperdal 111974-72-2, Seroquel 115103-54-3, Tiagabine 132539-06-1, Zyprexa 145821-59-6, Gabitril 146939-27-7, Geodon 148553-50-8, Pregabalin 148553-50-8D, Pregabalin, derivs.

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(limbic neurotransmission reduction-based method for treatment of clin. depression)

L91 ANSWER 131 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2005:140789 HCAPLUS

DOCUMENT NUMBER: 142:233347

TITLE: Compositions and methods for the treatment of depression and other affective disorders

INVENTOR(S): Dinan, Timothy; Daly, Peter

PATENT ASSIGNEE(S): Ire.

SOURCE: U.S. Pat. Appl. Publ., 9 pp.

CODEN: USXXCO

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2005037983	A1	20050217	US 2004-797146	20040311
WO 2005087207	A1	20050922	WO 2005-IB986	20050310
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW			
RW:	BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG			

PRIORITY APPLN: INFO.: US 2003-453786P P 20030311
 US 2003-459073P P 20030331
 US 2004-797146 A 20040311

AB The present invention relates to compns. and methods for treating

depression. The compns. and methods comprise the use of anti-inflammatory compds. alone or in combination with antidepressant compds. to down regulate HPA activation through the targeting of peripheral (non-CNS) cytokines.

IC ICM A61K031-7048
ICS A61K031-60; A61K031-405; A61K031-192; A61K031-225
INCL 514028000; 514570000; 514423000; 514460000; 514548000; 514165000;
514406000; 514420000
CC 1-11 (Pharmacology)
Section cross-reference(s): 63
IT **Mental disorder**
(affective; compns. and methods for treatment of **depression**
and other affective disorders)
IT **Mental disorder**
(bipolar disorder; compns. and methods for treatment of
depression and other affective disorders)
IT **Mental disorder**
(cyclothymia; compns. and methods for treatment of **depression**
and other affective disorders)
IT **Mental disorder**
(**depression**, drug-induced; compns. and methods for treatment
of **depression** and other affective disorders)
IT **Mental disorder**
(major **depression**; compns. and methods for treatment of
depression and other affective disorders)
IT **Mental disorder**
(neurotic **depression**; compns. and methods for treatment of
depression and other affective disorders)
IT 50-47-5, Desipramine 50-48-6, Amitriptyline 50-49-7, Imipramine
59-05-2, Methotrexate 64-19-7D, Acetic acid, Cyclic oxicams, biological
studies 69-72-7D, Salicylic acid, derivs. 72-69-5 79-09-4D,
Propionic acid, Aryl derivs. 113-53-1, Dosulepin 114-07-8,
Erythromycin 118-42-3, Hydroxychloroquine 118-92-3D, Anthranilic acid,
derivs. 155-09-9, Tranlylcypromine 288-13-1D, Pyrazole, derivs.
303-49-1 599-79-1, Sulfasalazine 739-71-9, Trimipramine 1668-19-5,
Doxepin 4498-32-2, Dibenzepin 5104-49-4, Flurbiprofen 10262-69-8,
Maprotiline 13710-19-5, Tolfenamic acid 15307-86-5, Diclofenac
15687-27-1, Ibuprofen 19794-93-5, Trazodone 21256-18-8, Oxaprozin
22071-15-4, Ketoprofen 22161-81-5, Dexketoprofen 22204-53-1, Naproxen
22494-42-4, Diflunisal 23979-41-1 24219-97-4, Mianserin 29679-58-1,
Fenoprofen 33005-95-7, Tiaprofen 34911-55-2, Bupropion 36330-85-5,
Fenbufen 36505-84-7, Buspirone 38194-50-2, Sulindac 42924-53-8,
Nabumetone 50537-15-0, (R)-Pirprofen 51146-56-6, Dexibuprofen
51146-57-7 51234-28-7, Benoxaprofen 51543-40-9, (R)-Flurbiprofen
51803-78-2, Nimesulide 52263-83-9, (R)-Carprofen 52780-13-9,
(R)-Suprofen 53086-14-9, (R)-Indoprofen 54739-18-3, Fluvoxamine
54910-89-3, Fluoxetine 56105-81-8 59729-33-8, Citalopram 59804-37-4,
Tenoxicam 61869-08-7, Paroxetine 63638-91-5, Brofaromine 66635-93-6,
(R)-Ketorolac 68693-11-8, Modafinil 70280-67-0, (R)-Benoxaprofen
71125-38-7, Meloxicam 71320-77-9, Moclobemide 71620-89-8, Reboxetine
74103-06-3, Ketorolac 75330-75-5, Lovastatin 79617-96-2, Sertraline
79902-63-9, Simvastatin 80214-83-1, Roxithromycin 81093-37-0,
Pravastatin 81103-11-9, Clarithromycin 83366-66-9, Nefazodone
83905-01-5, Azithromycin 85650-52-8, Mirtazapine 87226-41-3,
(R)-Etodolac 93413-69-5, Venlafaxine 93957-54-1, Fluvastatin
116539-59-4, Duloxetine 120210-48-2, Tenidap 128196-01-0,
Escitalopram 134523-00-5, Atorvastatin 162011-90-7, Rofecoxib
167933-07-5, Flibanserin 169590-42-5, Celecoxib 170277-31-3,
Infliximab 181695-72-7, Valdecoxib 185243-69-0, Etanercept

202409-33-4, Etoricoxib 331731-18-1, Adalimumab
RL: PAC (Pharmacological activity); THU (Therapeutic
use); BIOL (Biological study); USES (Uses)
(compns. and methods for treatment of depression and other
affective disorders)

L91 ANSWER 132 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2005:344028 HCAPLUS

DOCUMENT NUMBER: 143:90769

TITLE: The Monoamine-Mediated Antiallodynic Effects of
Intrathecally Administered Milnacipran, a Serotonin
Noradrenaline Reuptake Inhibitor, in a Rat Model of
Neuropathic Pain

AUTHOR(S): Obata, Hideaki; Saito, Shigeru; Koizuka, Shiro;
Nishikawa, Koichi; Goto, Fumio

CORPORATE SOURCE: Department of Anesthesiology, Gunma University
Graduate School of Medicine, Gunma, 371-8511, Japan

SOURCE: Anesthesia & Analgesia (Hagerstown, MD, United States)
(2005), 100(5), 1406-1410

CODEN: AACRAT; ISSN: 0003-2999

PUBLISHER: Lippincott Williams & Wilkins

DOCUMENT TYPE: Journal

LANGUAGE: English

AB **Antidepressants** are often used to treat neuropathic pain

. In the present study, we determined the antiallodynic effects of selective monoamine reuptake inhibitors in the spinal cord in a rat model of neuropathic pain. Mech. allodynia was produced by tight ligation of the left L5 and L6 spinal nerves and determined by applying von Frey filaments to the left hindpaw. A serotonin noradrenaline reuptake inhibitor, milnacipran, a selective serotonin reuptake inhibitor, paroxetine, or a selective noradrenaline reuptake inhibitor, maprotiline, was administered intrathecally via a chronically implanted catheter. Milnacipran produced dose-dependent antiallodynic effects at doses between 3 µg and 100 µg. The effect lasted for 7 h after injection of 100 µg ($P < 0.05$). The antiallodynic effect of 30 µg of milnacipran was attenuated by intrathecal coadministration of 30 µg of yohimbine, an α 2-adrenoceptor antagonist, 30 µg of methysergide, a serotonin receptor antagonist, or 30 µg of atropine, a muscarinic receptor antagonist ($P < 0.01$, resp.). I.p. administration of milnacipran had no antiallodynic effects at doses of 3 to 30 mg/kg. Antiallodynic effects were not produced by intrathecal administration of paroxetine (10 to 100 µg) or maprotiline (10 to 100 µg). These findings suggest that simultaneous inhibition of serotonin and noradrenaline reuptake in the spinal cord is essential to mediate antiallodynic effects. Milnacipran might be effective for suppression of neuropathic pain.

CC 1-11 (Pharmacology)

IT **Nervous system agents**

(noradrenaline reuptake inhibitors;

serotonin noradrenaline reuptake inhibitor milnacipran mediated dose-dependent antiallodynic effect in spinal nerve ligation which was attenuated by yohimbine, methylsergide and atropine at 30µg in rat with neuropathic pain)

REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 133 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2005:636971 HCAPLUS

DOCUMENT NUMBER: 143:360226

TITLE: Estrogen augmentation of antidepressants in

perimenopausal depression: a pilot study
AUTHOR(S): Morgan, Melinda L.; Cook, Ian A.; Rapkin, Andrea J.;
Leuchter, Andrew F.
CORPORATE SOURCE: Laboratory of Behavioral Pharmacology,
Neuropsychiatric Institute and Hospital, Department of
Psychiatry and Biobehavioral Sciences, University of
California Los Angeles, USA
SOURCE: Journal of Clinical Psychiatry (2005), 66(6), 774-780
CODEN: JCLPDE; ISSN: 0160-6689
PUBLISHER: Physicians Postgraduate Press, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Objective: To investigate the effects of estrogen augmentation on mood and
memory in women with perimenopausal depression who had experienced a
partial response to antidepressant medications. Method: In a
double-blind, placebo-controlled trial, 17 subjects taking antidepressant
medication were randomly assigned to either 0.625 mg/day of conjugated
estrogen (N = 11) or matching placebo (N = 6) for 6 wk. Women between the
ages of 40 and 60 years with DSM-IV major depressive disorder (MDD) in
partial remission who had been taking antidepressant medication for a min.
of 8 wk and were experiencing 1 or more perimenopausal symptoms (hot
flashes, night sweats, irregular periods, sleep disturbance, memory
impairment) were recruited from the community. The primary outcome
measures were the final scores for the Hamilton Rating Scale for
Depression (HAM-D) and the Buschke Selective Reminding Test. Data were
gathered from Apr. 2002 to August 2003. Results: Women receiving estrogen
had a significantly larger decrease in HAM-D scores than women receiving
placebo ($t = 2.86$, $df = 15$, $p = .012$). Group differences in tests of
verbal memory were not significant, although improved scores in verbal
memory were significantly correlated with a decrease in FSH ($p = .021$).
Conclusion: Short-term, low-dose estrogen augmentation of antidepressant
medication was significantly associated with improved mood, but not memory,
in perimenopausal women with MDD in partial remission.
CC 2-4 (Mammalian Hormones)
IT **Mental disorder**
(major **depression**; short term low dose estrogen augmentation
of antidepressant medication was significantly associated with improved
mood, but not memory, in perimenopausal women with major depressive
disorder in partial remission)
IT 34911-55-2, Bupropion 54910-89-3, Fluoxetine 59729-33-8, Citalopram
61869-08-7, Paroxetine 79617-96-2, Sertraline 93413-69-5,
Venlafaxine
RL: **PAC (Pharmacological activity); THU (Therapeutic
use); BIOL (Biological study); USES (Uses)**
(short term low dose estrogen augmentation of antidepressant medication
was significantly associated with improved mood, but not memory, in
perimenopausal women with major **depressive** disorder in
partial remission)
REFERENCE COUNT: 60 THERE ARE 60 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 134 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2005:550769 HCAPLUS
DOCUMENT NUMBER: 143:125657
TITLE: Duloxetine: Pharmacoeconomic implications of an
antidepressant that alleviates painful physical
symptoms
AUTHOR(S): McIntyre, Roger S.; Konarski, Jakub Z.
CORPORATE SOURCE: Department of Psychiatry, University of Toronto,

Toronto, ON, Can.
SOURCE: Expert Opinion on Pharmacotherapy (2005), 6(5),
707-713
CODEN: EOPHF7; ISSN: 1465-6566
PUBLISHER: Ashley Publications Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. Major depressive disorder (MDD) is a prevalent, chronic,
medical disorder that encompasses a broad constellation of symptoms. The
salience of painful phys. symptoms in depressive presentations is
increasingly appreciated. Duloxetine is a novel, potent, balanced, dual
monoamine reuptake-inhibitor antidepressant indicated for the symptomatic
relief of MDD. Duloxetine is marketed as an antidepressant that has
inherent analgesic properties for depressed patients who present with
prominent painful phys. symptoms. Taken together, available evidence
indicates that duloxetine provides a higher probability of, and shorter
time to, remission than some antidepressants (e.g., fluoxetine).
Duloxetine also offers symptom relief for painful phys. symptoms in
depressed patients. Pharmacoeconomic and cost-impact modeling analyses
should be reformulated to consider duloxetine's symptom-alleviating effect
on the somatic dimension of depressive illness.
CC 1-0 (Pharmacology)
IT **Mental disorder**
(major **depression**; duloxetine alleviated painful phys.
symptoms and improved remission in major depressive disorder patient)
IT 116539-59-4, Duloxetine
RL: PAC (Pharmacological activity); THU (Therapeutic
use); BIOL (Biological study); USES (Uses)
(duloxetine alleviated painful phys. symptoms and improved remission in
major **depressive** disorder patient)
REFERENCE COUNT: 65 THERE ARE 65 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 135 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2005:365187 HCAPLUS
DOCUMENT NUMBER: 143:126485
TITLE: Effects of antidepressant treatment and of gender on
serum leptin levels in patients with major depression
AUTHOR(S): Esel, Ertugrul; Ozsoy, Saliha; Tutus, Ahmet; Sofuoglu,
Seher; Kartalci, Sukru; Bayram, Fahri; Kokbudak,
Zaliha; Kula, Mustafa
CORPORATE SOURCE: Department of Psychiatry, Erciyes University School of
Medicine, Kayseri, 38039, Turk.
SOURCE: Progress in Neuro-Psychopharmacology & Biological
Psychiatry (2005), 29(4), 565-570
CODEN: PNPPD7; ISSN: 0278-5846
PUBLISHER: Elsevier B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Leptin is a product of the obese gene and plays an important role in the
regulation of body weight and food intake. Weight and appetite are frequently
altered in depression. So far, inconsistent results have been reported in
terms of leptin levels in depression. Therefore, the authors investigated
serum leptin levels in patients with depression and in healthy controls,
and whether there was any alteration throughout antidepressant treatment.
Female patients showed significantly higher leptin levels than those of
the control females both before and after the response to antidepressant
treatment, whereas no difference was found between the male patients and
the male controls. The improvement from depression with antidepressant

treatment caused a further elevation on the leptin levels, in both female and male patients. These findings confirm an increase in leptin levels in depressive patients and presence of a sexual dimorphism. Moreover, clin. response to antidepressant treatment seems to have an addnl. increasing effect on leptin levels.

CC 1-11 (Pharmacology)

IT **Mental disorder**

(**depression**; female patients showed higher serum leptin levels while no difference in males before antidepressant treatment and antidepressant treatment caused further elevation on leptin levels in both female and male patients with major **depression**)

IT 93413-69-5, Venlafaxine

RL: **PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)**

(female patients showed higher serum leptin levels while no difference in males both before and after antidepressant treatment including venlafaxine caused further elevation on leptin levels in both patients with major **depression**)

REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 136 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2005:431911 HCAPLUS

DOCUMENT NUMBER: 143:126539

TITLE: Olanzapine increases slow wave sleep and sleep continuity in SSRI-resistant depressed patients

AUTHOR(S): Sharpley, Ann L.; Attenburrow, Mary E. J.; Hafizi, Sepehr; Cowen, Philip J.

CORPORATE SOURCE: Warneford Hospital, University Department of Psychiatry, Oxford, UK

SOURCE: Journal of Clinical Psychiatry (2005), 66(4), 450-454
CODEN: JCLPDE; ISSN: 0160-6689

PUBLISHER: Physicians Postgraduate Press, Inc.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The atypical antipsychotic drug olanzapine has been employed as an augmentation treatment in depressed patients unresponsive to treatment with selective serotonin reuptake inhibitors (SSRIs). In healthy subjects, acute olanzapine administration increases sleep continuity and enhances slow wave sleep (SWS). The aim of the present study was to determine if the addition of olanzapine to SSRI treatment in depressed patients produced similar effects on sleep. We measured the effect of open-label olanzapine addition (2.5 mg/day initially) on the polysomnograms of 12 patients referred from primary care sources who met DSM-IV criteria for major depressive disorder and who had had an unsatisfactory response to therapeutic doses of an SSRI. Patients were first enrolled in Nov. 2001; final assessment occurred in Nov. 2003. Sleep polysomnogram recordings were made on 3 occasions: before olanzapine addition, on the first night of olanzapine treatment, and after 3 wk of olanzapine treatment. After the first night of olanzapine treatment and during the third week, subjects showed improvements in sleep efficiency ($p < .001$), subjective sleep quality ($p < .05$), and SWS ($p < .01$). Scores on the Hamilton Rating Scale for Depression fell significantly ($p = .001$), with the majority of the decrease being apparent after the first week of treatment. Conclusion: Olanzapine improves sleep continuity and increases SWS in patients receiving SSRI treatment. These effects are apparent after the first dose of olanzapine and are maintained for the next 3 wk. The ability of olanzapine to increase SWS is probably attributable to 5-HT_{2A/2C} receptor blockade, which has been identified as a relevant mechanism in the

therapeutic effect of olanzapine in SSRI-resistant depressed patients.
CC 1-11 (Pharmacology)
IT **Mental disorder**
(depression; effect of olanzapine addition to SSRI treatment on
sleep in depressed patients)
IT 54910-89-3, Fluoxetine 59729-33-8, Citalopram 61869-08-7, Paroxetine
79617-96-2, Sertraline 93413-69-5, Venlafaxine
RL: **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(effect of olanzapine addition to SSRI treatment on sleep in
depressed patients)
REFERENCE COUNT: 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 137 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2005:528480 HCAPLUS
DOCUMENT NUMBER: 143:241145
TITLE: **Antidepressants** in the treatment of
neuropathic **pain**
AUTHOR(S): Sindrup, Soren H.; Otto, Marit; Finnerup, Nanna B.;
Jensen, Troels S.
CORPORATE SOURCE: Department of Neurology, Odense University Hospital,
Odense, Den.
SOURCE: Basic & Clinical Pharmacology & Toxicology (2005),
96(6), 399-409
CODEN: BCPTBO; ISSN: 1742-7835
PUBLISHER: Blackwell Publishing Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. Neuropathic pain is due to lesion or dysfunction of the
peripheral or central nervous system. Tricyclic antidepressants and
anticonvulsants have long been the mainstay of treatment of this type of
pain. Tricyclic **antidepressants** may relieve neuropathic
pain by their unique ability to inhibit presynaptic reuptake of
the biogenic amines serotonin and noradrenaline, but other mechanisms such
as N-methyl-D-aspartate receptor and ion channel blockade probably also
play a role in their pain-relieving effect. The effect of tricyclic
antidepressants in neuropathic **pain** in man has been
demonstrated in numerous randomized, controlled trials, and a few trials
have shown that serotonin noradrenaline and selective serotonin reuptake
inhibitor **antidepressants** also relieve neuropathic **pain**
although with lower efficacy. Tricyclic antidepressants will relieve one
in every 2-3 patients with peripheral neuropathic pain, serotonin
noradrenaline reuptake inhibitors one in every 4-5, and selective
serotonin reuptake inhibitors one in every 7 patients. Thus, based on
efficacy measures such as nos. needed to treat, tricyclic antidepressants
tend to work better than the anticonvulsant gabapentin and treatment
options such as tramadol and oxycodone, whereas the serotonin
noradrenaline reuptake inhibitor venlafaxine appears to be equally
effective with these drugs and selective serotonin reuptake inhibitors
apparently have lower efficacy. Head-to-head comparisons between
antidepressants and the other analgesics are lacking. Contraindications
towards the use of tricyclic antidepressants and low tolerability in
general of this drug class may among the antidepressants favor the use of
the serotonin noradrenaline reuptake inhibitors. A recent study on
bupropion, which is a noradrenaline and dopamine uptake inhibitor,
indicated a surprisingly high efficacy of this drug in peripheral
neuropathic pain. In conclusion, **antidepressants** represent
useful tools in neuropathic **pain** treatment and must still be
considered as first-line treatments of neuropathic pain. However, without

head-to-head comparisons between antidepressants and other analgesics, it is not possible to provide real evidence-based treatment algorithms for neuropathic pain.

CC 1-0 (Pharmacology)

Section cross-reference(s): 14

ST review **antidepressant** neuropathic pain

IT 5-HT reuptake inhibitors

Analgesics

Anticonvulsants

Antidepressants

Human

(**antidepressants** in treatment of neuropathic pain)

IT **Pain**

(neuropathic; **antidepressants** in treatment of neuropathic pain)

IT **Nervous system agents**

(**noradrenaline reuptake inhibitors**;

antidepressants in treatment of neuropathic pain)

REFERENCE COUNT: 71 THERE ARE 71 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 138 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2005:93509 HCAPLUS

DOCUMENT NUMBER: 142:404000

TITLE: Remarkable effect of milnacipran, a serotonin-noradrenalin reuptake inhibitor (SNRI), on depressive symptoms in patients with Parkinson's disease who have insufficient response to selective serotonin reuptake inhibitors (SSRIs): two case reports

AUTHOR(S): Takahashi, Hitoshi; Kamata, Mitsuhiro; Yoshida, Keizo; Higuchi, Hisashi; Shimizu, Tetsuo

CORPORATE SOURCE: Department of Neuropsychiatry, Akita University School of Medicine, Hondo, Akita, 010-8543, Japan

SOURCE: Progress in Neuro-Psychopharmacology & Biological Psychiatry (2005), 29(2), 351-353
CODEN: PNPPD7; ISSN: 0278-5846

PUBLISHER: Elsevier B.V.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The authors present here two cases of Parkinson's disease with depression refractory to SSRIs treatment, who experienced a complete remission after replacing the ongoing SSRIs with a serotonin-noradrenalin reuptake inhibitor (SNRI), milnacipran. The case reports suggest that milnacipran may be one of the treatment options for depression in patients with Parkinson's disease who had inadequate response to SSRIs. Further studies are warranted to confirm this observation.

CC 1-11 (Pharmacology)

IT **Mental disorder**

(**depression**; serotonin-noradrenalin reuptake inhibitor milnacipran remitted all depressive symptoms without worsening Parkinsonian symptoms in patient with PD who had insufficient response to selective serotonin reuptake inhibitors)

IT 92623-85-3, Milnacipran

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(serotonin-noradrenalin reuptake inhibitor milnacipran remitted all **depressive** symptoms without worsening Parkinsonian symptoms in patient with PD who had insufficient response to selective serotonin

reuptake inhibitors)

REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 139 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2005:674132 HCAPLUS

TITLE: Duloxetine for the treatment of major depressive
disorder in women ages 40 to 55 yearsAUTHOR(S): Burt, Vivien K.; Wohlreich, Madelaine M.;
Mallinckrodt, Craig H.; Detke, Michael J.; Watkin,
John G.; Stewart, Donna E.CORPORATE SOURCE: The Department of Psychiatry and Biobehavioral
Sciences, UCLA School of Medicine, Los Angeles, USA

SOURCE: Psychosomatics (2005), 46(4), 345-354

CODEN: PSYCBC; ISSN: 0033-3182

PUBLISHER: American Psychiatric Publishing, Inc.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The efficacy of duloxetine in the treatment of major depressive disorder in women of approx. perimenopausal age (40-55 years; 62 placebo subjects and 55 subjects taking duloxetine, 60 mg/day) was compared with that observed in cohorts of younger (<40 years, 94 placebo subjects and 85 duloxetine subjects) and older (>55 years, 26 placebo subjects and 25 duloxetine subjects) women. Women (ages 40-55 years) receiving duloxetine demonstrated significantly greater improvement in total scores on the 17-item Hamilton Rating Scale for Depression compared with placebo at the study endpoint (week 9). Significant advantages for duloxetine over placebo were observed on 17-item Hamilton depression scale subscales (core, Maier, anxiety, retardation, and sleep), in addition to the Clin. Global Impression severity and Patient Global Impression of Improvement Scale, the Quality of Life in Depression Scale, and Visual Analog Scales assessing pain severity. The magnitude of duloxetine's treatment effect in women ages 40-55 years was similar to that observed in younger (age <40 years) and older (age >55 years) female patients. In the placebo treatment groups, however, mean changes differed substantially by age group with the smallest placebo responses observed in the 40-55 age group. Duloxetine (60 mg/day) was demonstrated to be an effective treatment for major depressive disorder in this cohort of women ages 40-55 years.

CC 1 (Pharmacology)

ST duloxetine **serotonin norepinephrine reuptake inhibitor** major depressive disorder

IT INDEXING IN PROGRESS

IT 5-HT **reuptake inhibitors**

Human

(dual **reuptake inhibitor** of **serotonin** and **norepinephrine**, duloxetine was effective for treatment of major depressive disorder in women ages 40- 55 years)

IT Pain

(duloxetine effectively improved severity of overall **pain**, headache, shoulder **pain**, amount of time in **pain** in major **depressive** disorder patient ages 40- 55 years)

IT Mental disorder

(major depression; dual **reuptake inhibitor** of **serotonin** and **norepinephrine**, duloxetine was effective for treatment of major depressive disorder in women ages 40- 55 years)

IT Nervous system agents

(noradrenaline **reuptake inhibitors**; dual

**reuptake inhibitor of serotonin and
norepinephrine**, duloxetine was effective for treatment of major
depressive disorder in women ages 40- 55 years)

REFERENCE COUNT: 57 THERE ARE 57 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 140 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2005:439197 HCAPLUS
DOCUMENT NUMBER: 143:185910
TITLE: Efficacy, safety and tolerability of duloxetine 60 mg
once daily in major depression
AUTHOR(S): Cowen, Philip J.; Ogilvie, Alan D.; Gama, Joubert
CORPORATE SOURCE: Department of Psychiatry, Warneford Hospital,
University of Oxford, Oxford, UK
SOURCE: Current Medical Research and Opinion (2005), 21(3),
345-355
CODEN: CMROCX; ISSN: 0300-7995
PUBLISHER: LibraPharm Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. Major depressive disorders (MDD) present a significant public health problem, in terms of burden for individual sufferers, their families and society as a whole. Recently, dual-acting antidepressants, which block both serotonin (5-HT) and noradrenaline (NA) reuptake, have been developed with the hope of improving depression treatment outcomes. Duloxetine is a dual reuptake inhibitor of 5-HT and NA that has recently been licensed in the USA for the treatment of MDD. This paper summarizes efficacy and tolerability data for duloxetine with particular reference to the dose recommended for clin. use - 60 mg once daily. Papers relating to duloxetine 60 mg once daily were identified through Medline searches and the publication databases at Eli Lilly/Boehringer Ingelheim. Randomized, placebo-controlled studies have demonstrated the efficacy of duloxetine 60 mg once daily for the treatment of depression in the short and long term. Thus, duloxetine 60 mg once daily was superior to placebo in reducing MDD symptoms according to the primary efficacy measure - the 17-item Hamilton Depression Rating Scale (HAMD). Significantly greater improvements in subfactors of HAMD and quality of life measures were also seen. In addition, duloxetine has been shown significantly to reduce the general aches and pains that frequently accompany MDD. A recent placebo-controlled study demonstrated that duloxetine improved cognition and depression measures in depressed elderly patients. Duloxetine appears to have an acceptable tolerance. The most frequently observed adverse events with duloxetine were nausea, dry mouth and somnolence. Importantly, duloxetine did not appear to have a clin. significant effect on blood pressure. In summary, duloxetine 60 mg once daily is effective for the treatment of core depressive symptoms, as well as general aches and pains associated with depression.

CC 1-0 (Pharmacology)

IT **Mental disorder**

(major depression; duloxetine in major depression)

IT 116539-59-4, Duloxetine

RL: ADV (Adverse effect, including toxicity); DMA (Drug mechanism of action); PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(duloxetine in major depression)

REFERENCE COUNT: 70 THERE ARE 70 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 141 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN
 ACCESSION NUMBER: 2005:244884 HCAPLUS
 DOCUMENT NUMBER: 143:53309
 TITLE: Do venlafaxine XR and paroxetine equally influence
 negative and positive affect?
 AUTHOR(S): Dichter, Gabriel S.; Tomarken, Andrew J.; Freid,
 Cathryn M.; Addington, Stephanie; Shelton, Richard C.
 CORPORATE SOURCE: Department of Psychology, College of Arts and
 Sciences, Vanderbilt University, Nashville, TN, 37203,
 USA
 SOURCE: Journal of Affective Disorders (2005), 85(3), 333-339
 CODEN: JADID7; ISSN: 0165-0327
 PUBLISHER: Elsevier Ltd.
 DOCUMENT TYPE: Journal
 LANGUAGE: English

AB Background: We assessed the therapeutic effects of venlafaxine XR and
 paroxetine on mood and anxiety symptoms derived from the tripartite model
 of mood. We hypothesized that the two antidepressants would have largely
 similar effects on symptoms of neg. affect because both agents influence
 serotonergic systems. However, based on evidence indicating linkages
 between catecholaminergic activity and the emotional dimension of pos.
 affect, we hypothesized that the catecholaminergic effects of venlafaxine
 XR would yield particularly pronounced effects on symptoms of pos. affect.
 Methods: Twenty depressed outpatients were randomly assigned to treatment
 with either venlafaxine XR (225 mg/day) or paroxetine (30 mg/day) during a
 12-wk treatment trial. Weekly mood ratings were collected using the Mood
 and Anxiety Symptom Questionnaire [Watson, D., Clark, L.A., Weber, K.,
 Assenheimer, J.S., Strauss, M.E., McCormick, R.A., 1995. Testing a
 tripartite model: II. Exploring the symptom structure of anxiety and
 depression in student, adult, and patient samples. J. Abnorm. Psychol. 104
 (1), 15-25] [Watson, D., Weber, K., Assenheimer, J.S., Clark, L.A.,
 Strauss, M.E., McCormick, R.A., 1995. Testing a tripartite model: I.
 Evaluating the convergent and discriminant validity of anxiety and
 depression symptom scales. J. Abnorm. Psychol. 104 (1), 3-14]. Results:
 Consistent with predictions, analyses revealed that there were no
 significant differences between venlafaxine XR and paroxetine on measures
 of neg. affect. However, contrary to predictions, the two medications
 produced similar changes on measures of pos. affect. Limitations:
 Replication and extension using a larger sample size are mandated.
 Conclusions: These preliminary results suggest that two antidepressants
 that appear to have dissimilar mechanisms of action may nevertheless have
 similar effects on the pos. and neg. affective components of depression.
 Alternatively, paroxetine may have a clin. relevant noradrenergic effect
 at the dose tested.

CC 1-11 (Pharmacology)

IT **Mental disorder**

(anhedonia; venlafaxine XR and paroxetine are equally effective
 antidepressants having robust effects on symptoms of **depression**
 , anxiety, and anhedonia in a depressed outpatient)

IT **Mental disorder**

(**depression**; venlafaxine XR and paroxetine are equally
 effective antidepressants having robust effects on symptoms of
depression, anxiety, and anhedonia in a depressed outpatient)

IT 61869-08-7, Paroxetine 93413-69-5, Venlafaxine

RL: PAC (Pharmacological activity); THU (Therapeutic
 use); BIOL (Biological study); USES (Uses)

(venlafaxine XR and paroxetine are equally effective antidepressants
 having robust effects on symptoms of **depression**, anxiety, and
 anhedonia in a **depressed** outpatient)

REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 142 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2005:513424 HCAPLUS

DOCUMENT NUMBER: 143:298911

TITLE: Acute tryptophan depletion in depressed patients
treated with a selective serotonin-noradrenalin
reuptake inhibitor: Augmentation of antidepressant
response?

AUTHOR(S): Booij, Linda; Van der Does, A. J. Willem; Haffmans, P.
M. Judith; Riedel, Wim J.

CORPORATE SOURCE: Department of Psychology, Leiden University, Leiden,
2333 AK, Neth.

SOURCE: Journal of Affective Disorders (2005), 86(2-3),
305-311

CODEN: JADID7; ISSN: 0165-0327

PUBLISHER: Elsevier Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Background: It has frequently been demonstrated that exptl. lowering of
serotonin (5-HT) neurotransmission by acute tryptophan depletion (ATD)
induces a transient depressed mood in 50-60% of patients treated with a
selective serotonin reuptake inhibitor (SSRI) who are in remission from
depression. In unmedicated depressed patients, ATD has no immediate
effect on symptoms. The effects in currently depressed medicated patients
have not been investigated. Methods: Fourteen currently depressed
patients (seven patients treated with a selective serotonin-noradrenalin
reuptake inhibitor (SSNRI); seven other treatment, non-SSNRI) received ATD
in a double-blind, crossover design. Different strengths of the ATD mixture
(aimed at 50% and 90% reduction of tryptophan) were used on sep. days.
Psychiatric symptoms were assessed at both sessions prior to, at +6.5 h,
and at +24 h after ATD. Results: The ATD mixts. induced the expected
redns. of plasma tryptophan levels. Full but not partial depletion
improved mood and other psychiatric symptoms at +24 h in patients who
received SSNRI treatment, as indicated by clin. ratings and self-report.
Subjective sleep quality also improved. Conclusions: The effects of ATD
on psychiatric symptoms in currently depressed patients are remarkably
different from the results in recently remitted SSRI-treated patients.
ATD in currently depressed patients treated with serotonergic
antidepressants possibly provides important information about the
mechanism of action of SSRIs.

CC 1-11 (Pharmacology)

IT **Mental disorder**

(**depression**; acute tryptophan depletion improved sleep
quality, mood, other psychiatric symptoms and reduced plasma tryptophan
level in depressed patient treated with selective serotonin-
noradrenalin reuptake inhibitors compared to non-SSNRIs)

IT 7439-93-2, Lithium, biological studies 93413-69-5, Venlafaxine

RL: **PAC (Pharmacological activity); THU (Therapeutic
use); BIOL (Biological study); USES (Uses)**

(acute tryptophan depletion improved sleep quality, mood, other
psychiatric symptoms and reduced plasma tryptophan level in
depressed patient treated with selective serotonin-noradrenalin
reuptake inhibitor venlafaxine compared to non-SSNRIs)

REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 143 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2005:93498 HCAPLUS
DOCUMENT NUMBER: 142:423559
TITLE: The effect of chronic antidepressant treatment on serum brain-derived neurotrophic factor levels in depressed patients: a preliminary study
AUTHOR(S): Aydemir, Omer; Deveci, Artuner; Taneli, Fatma
CORPORATE SOURCE: Department of Psychiatry, Faculty of Medicine, Celal Bayar University, Manisa, 45010, Turk.
SOURCE: Progress in Neuro-Psychopharmacology & Biological Psychiatry (2005), 29(2), 261-265
CODEN: PNPPD7; ISSN: 0278-5846
PUBLISHER: Elsevier B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Recent studies suggested a role of brain-derived neurotrophic factor (BDNF) in depression. While BDNF levels are lower in depressed patients, antidepressant treatment increases serum BDNF levels of depressed patients. Our study aims to test the effect of chronic venlafaxine treatment on serum BDNF levels in patients with a major depressive disorder. Ten patients diagnosed as major depressive disorder according to DSM-IV are included in the study. Two of the patients had their first episode and were drug-naive, the other eight patients were drug-free for at least 4 wk. The severity of depression was assessed with Hamilton Depression Rating Scale (HDRS). The control group consisted of ten age- and sex-matched subjects without any psychiatric disorder. Blood samples were collected at the baseline and after 12 wk of antidepressant treatment (during remission). At the baseline the mean serum BDNF level was 17.9 ± 9.1 ng/mL and the mean HDRS score was 23.2 ± 4.6 . Serum BDNF levels of the study group were significantly lower than in the control group (31.6 ± 8.6 ng/mL). At the end of the study, the mean serum BDNF level was 34.6 ± 7.1 ng/mL whereas the mean HDRS score was 8.2 ± 3.9 . From the baseline to the remission after 12 wk of treatment, the increase in serum BDNF level and the decrease in HDRS score were statistically significant, resp. When we compared the serum BDNF level of depressed patients at remission to that of the controls, there was no statistically significant difference. This study shows that venlafaxine treatment of depression improves serum BDNF level which may be considered as a nonspecific peripheral marker of depression.

CC 1-11 (Pharmacology)
IT **Mental disorder**
(major depression; chronic antidepressant venlafaxine treatment improved serum brain-derived neurotrophic factor level in major depressive disorder patient)

IT 93413-69-5, Venlafaxine
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study);
USES (Uses)
(chronic antidepressant venlafaxine treatment improved serum brain-derived neurotrophic factor level in depressed patient)

REFERENCE COUNT: 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 144 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2005:109452 HCAPLUS
DOCUMENT NUMBER: 142:423573
TITLE: Bupropion and venlafaxine responders differ in pretreatment regional cerebral metabolism in unipolar depression
AUTHOR(S): Little, John T.; Ketter, Terence A.; Kimbrell, Tim A.;

Dunn, Robert T.; Benson, Brenda E.; Willis, Mark W.; Luckenbaugh, David A.; Post, Robert M.
CORPORATE SOURCE: Division of Psychiatric Neuroimaging, Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, MD, USA
SOURCE: Biological Psychiatry (2005), 57(3), 220-228
CODEN: BIPCBF; ISSN: 0006-3223
PUBLISHER: Elsevier Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Pretreatment functional brain imaging was examined for never-hospitalized outpatients with unipolar depression compared with control subjects in a crossover treatment trial involving bupropion or venlafaxine monotherapy. Patients (n = 20) with unipolar depression received baseline (medication-free) fluorine-18 deoxyglucose (FDG) positron emission tomog. (PET) scan and then at least 6 wk of bupropion or venlafaxine monotherapy in a single-blind crossover trial. Age-matched healthy control subjects (n = 20) also received baseline FDG PET scans. For each medication PET data from patients compared with control subjects was analyzed as a function of treatment response (defined as moderate to marked improvement on the Clin. Global Impression Scale). Treatment response rates were similar for bupropion (32%) and venlafaxine (33%). Compared with control subjects, responders but not nonresponders, to both drugs demonstrated frontal and left temporal hypometabolism. Selectively, compared with control subjects bupropion responders (n = 6) also had cerebellar hypermetabolism, whereas venlafaxine responders (n = 7) showed bilateral temporal and basal ganglia hypometabolism. These data suggest that pretreatment frontal and left temporal hypometabolism in never-hospitalized depressed outpatients compared with control subjects is linked to pos. antidepressant response and that addnl. alterations in regional metabolism may be linked to differential responsivity to bupropion and venlafaxine monotherapy.
CC 1-11 (Pharmacology)
IT **Mental disorder**
(unipolar **depression**; bupropion, venlafaxine show response rate, frontal, left temporal hypometabolism, bupropion responder had cerebellar hypermetabolism, venlafaxine responder had bilateral temporal, basal ganglia hypometabolism in unipolar **depression** patient)
IT **93413-69-5, Venlafaxine**
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study);
USES (Uses)
(venlafaxine showed similar response rates, frontal, left temporal hypometabolism with venlafaxine responder showing bilateral temporal, basal ganglia hypometabolism in patient with unipolar **depression**)
REFERENCE COUNT: 51 THERE ARE 51 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT
L91 ANSWER 145 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2005:1022882 HCAPLUS
TITLE: Time course of depression-symptom improvement during treatment with duloxetine
AUTHOR(S): Hirschfeld, Robert M. A.; Mallinckrodt, Craig; Lee, Thomas C.; Detke, Michael J.
CORPORATE SOURCE: University of Texas Medical Branch, Galveston, TX, USA
SOURCE: Depression and Anxiety (2005), 21(4), 170-177
CODEN: DEANF5; ISSN: 1091-4269

PUBLISHER: Wiley-Liss, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The aim of this study was to examine the longitudinal response for overall and individual symptoms during the treatment of major depressive disorder. Data were pooled from two 9-wk trials, which compared duloxetine 60-mg QD (n = 251) with placebo (n = 261) in the treatment of MDD. Changes from baseline in the 17-item Hamilton Depression Rating Scale (HAM-D17) and in the Visual Analog Scales for pain were analyzed. Compared to placebo-treated patients, duloxetine-treated patients experienced greater improvement ($P < .05$) in the HAM-D17 total score at Week 2. The individual symptoms showing the most rapid improvements (Week 1) were depressed mood, guilt, suicidal ideation, work/activities, and psychic anxiety as well as VAS back pain and shoulder pain. At subsequent visits, significant improvements were observed in retardation (Week 2); hypochondriasis (Week 3); general somatic symptoms (Week 5); middle and late insomnia (Week 7); and gastrointestinal (GI) symptoms, genital symptoms (level of sexual interest or ease of sexual arousal), insight, and early insomnia (Week 9). Significant advantages for duloxetine were not achieved at any visit for agitation, somatic anxiety, or weight loss. At Weeks 1 and 2, placebo-treated patients had significantly lower GI symptoms and reported less weight loss compared with duloxetine-treated patients; however, differences were not significant at subsequent visits. Furthermore, duloxetine was superior to placebo on GI symptoms at endpoint compared to placebo-treated patients; duloxetine-treated patients had a significantly higher response rate at Week 2 and a higher remission rate at Week 5. These results may help clinicians establish more accurate expectations regarding treatment with duloxetine.

CC 1 (Pharmacology)

ST major depressive disorder duloxetine serotonin
norepinephrine reuptake inhibitor; hydroxy
tryptamine

IT INDEXING IN PROGRESS

IT Human

(duloxetine showed rapid improvement in symptoms like mood, guilt, work/activities, retardation, hypochondriasis, slower response were achieved for sleep, genital and nonpainful somatic symptoms in patient with major depressive disorder)

IT Mental disorder

(major depression; duloxetine showed rapid improvement in symptoms like mood, guilt, work/activities, retardation, hypochondriasis, slower response were achieved for sleep, genital and nonpainful somatic symptoms in patient with major depressive disorder)

IT Nervous system agents

(noradrenaline reuptake inhibitors;
norepinephrine reuptake inhibitor duloxetine was effective and showed greater improvement in symptoms of patient with major depressive disorder)

REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 146 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2005:269489 HCAPLUS

DOCUMENT NUMBER: 143:149

TITLE: The safety of newer antidepressants in pregnancy and breastfeeding

AUTHOR(S): Gentile, Salvatore

CORPORATE SOURCE: Department of Mental Health, ASL Salerno 1, Cava de' Tirreni, Italy

SOURCE: Drug Safety (2005), 28(2), 137-152
 CODEN: DRSAEA; ISSN: 0114-5916
 PUBLISHER: Adis International Ltd.
 DOCUMENT TYPE: Journal; General Review
 LANGUAGE: English

AB A review. The pregnancy and postpartum periods are considered to be relatively high risk times for depressive episodes in women, particularly for those with pre-existing psychiatric illnesses. Therefore, it may be necessary to start or continue the pharmacol. treatment of depression during these two timeframes. Hence, the aim of this review is to examine the effects on the fetus and infant of exposure, through the placenta and maternal milk, to the following drugs: fluoxetine, fluvoxamine, paroxetine, sertraline, citalopram, escitalopram, mirtazapine, venlafaxine, reboxetine and bupropion. The teratogenic risks, perinatal toxicity and effects on the neurobehavioural development of newborns associated with exposure through the placenta or maternal milk to these medications need to be carefully assessed before starting psychopharmacol. treatment in pregnant or lactating women. In spite of the limitations of some of the studies reviewed, the older selective serotonin-reuptake inhibitors (SSRIs) [as we await further data regarding escitalopram] and venlafaxine seem to be devoid of teratogenic risks. By contrast, the data concerning possible consequences related to exposure to SSRIs via the placenta and breastmilk on neonatal adaptation and long-term neurocognitive infant's development are still controversial. Nevertheless, a number of reports have shown that an association between placental exposure to SSRIs and adverse but self-limiting effects on neonatal adaptation may exist. In addition, the information on both teratogenic and functional teratogenic risks associated with exposure to bupropion, mirtazapine and reboxetine is incomplete or absent; at present, these compds. should not be used as first-line agents in the pharmacol. treatment of depression in pregnancy and breastfeeding. Untreated depression is not without its own risks since mothers affected by depression have a neg. impact on the emotional development of their children and major depression, especially when complicated by a delusional component, may lead to the mother attempting suicide and infanticide. Consequently, clinicians need to help mothers weigh the risks of prenatal exposure to drugs for their babies against the potential risks of untreated depression and abrupt discontinuation of pharmacol. treatment. Given these situations, we suggest that choosing to administer psychopharmacol. treatment in pregnant or breastfeeding women with depression will result primarily from a careful evaluation of their psychopathol. condition; currently, the degree of severity of maternal disease appears to represent the most relevant parameter to take this clin. decision.

CC 1-0 (Pharmacology)

IT **Mental disorder**

(mood-affecting; careful evaluation of psychopathol. condition, disease severity serve as most relevant parameter in selecting psychopharmacol. treatment with antidepressant in pregnant and breastfeeding woman with **depression** and mood disorder)

IT **Mental disorder**

(postpartum **depression**; careful evaluation of psychopathol. condition, disease severity serve as most relevant parameter in selecting psychopharmacol. treatment with antidepressant in pregnant and breastfeeding woman with **depression** and mood disorder)

IT 93413-69-5, Venlafaxine

RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(careful evaluation of psychopathol. condition, disease severity serve as most relevant parameter in selecting psychopharmacol. treatment with venlafaxine in pregnant and breastfeeding woman with **depression** and mood disorders)

REFERENCE COUNT: 144 THERE ARE 144 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE
FORMAT

L91 ANSWER 147 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2005:173368 HCAPLUS

DOCUMENT NUMBER: 143:71488

TITLE: Cardiovascular Profile of Duloxetine, a Dual Reuptake Inhibitor of Serotonin and Norepinephrine

AUTHOR(S): Thase, Michael E.; Tran, Pierre V.; Wiltse, Curtis; Pangallo, Beth A.; Mallinckrodt, Craig; Detke, Michael J.

CORPORATE SOURCE: Department of Psychiatry, University of Pittsburgh Medical Center, Western Psychiatric Institute and Clinic, Pittsburgh, PA, USA

SOURCE: Journal of Clinical Psychopharmacology (2005), 25(2), 132-140

CODEN: JCPYDR; ISSN: 0271-0749

PUBLISHER: Lippincott Williams & Wilkins

DOCUMENT TYPE: Journal

LANGUAGE: English

AB This anal. assessed the effects of duloxetine, a dual reuptake inhibitor of serotonin and norepinephrine, on indexes of cardiovascular safety, including heart rate, blood pressure (BP), and electrocardiograms (ECGs), in a large group of clin. trial patients with depression. Data were available from 8 double-blind, randomized, placebo-controlled (n = 777), and active comparator-controlled depression trials. Duloxetine (n = 1139) doses ranged from 40 to 120 mg/d, and fluoxetine (n = 70) and paroxetine (n = 359) were administered at a dose of 20 mg/d. Patients were treated for 8 to 9 wk. There was a significant increase for duloxetine compared with placebo for heart rate (1.6 vs. -0.6 beats per min) and for systolic BP (1.0 vs. -1.2 mm Hg); the difference for diastolic BP (1.1 vs. 0.3) was not significant. There were no significant differences between duloxetine and placebo treatment groups in the incidence of sustained (at least 3 consecutive visits) elevations in systolic (duloxetine 1.0%, placebo 0.4%), diastolic (duloxetine 0.4%, placebo 0.4%), or either (duloxetine 1.3%, placebo 0.8%) BP. Moreover, the effect of duloxetine on mean changes in supine systolic and diastolic BP was not significantly different from that of fluoxetine or paroxetine. Drug-placebo differences in mean changes in electrocardiograms (eg, QTc, PR, and QRS intervals) were neither statistically nor clin. significant, with the exception that duloxetine 120 mg/d had significant decreases in PR and QRS intervals compared with placebo. These data demonstrate that duloxetine has modest effects on heart rate and BP and no clin. meaningful effect on ECG profiles in a relatively healthy cohort of clin. trial patients. The cardiovascular effects of duloxetine appear to be comparable with medications considered to be first-line options for depression.

CC 1-11 (Pharmacology)

IT **Mental disorder**

(major **depression**; duloxetine showed modest effect on heart rate and blood pressure while no clin. meaningful effect on ECG profile was seen in major depressive disorder patient)

IT 136434-34-9, Cymbalta

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(duloxetine showed modest effect on heart rate and blood pressure while no clin. meaningful effect on ECG profile was seen in major depressive disorder patient)

REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 148 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2005:544090 HCAPLUS

DOCUMENT NUMBER: 143:359867

TITLE: Is treatment-associated hypomania rare with duloxetine: Secondary analysis of controlled trials in non-bipolar depression

AUTHOR(S): Dunner, David L.; D'Souza, Deborah N.; Kajdasz, Daniel K.; Detke, Michael J.; Russell, James M.

CORPORATE SOURCE: Department of Psychiatry and Behavioral Sciences, University of Washington Center for Anxiety and Depression, Seattle, WA, 98105, USA

SOURCE: Journal of Affective Disorders (2005), 87(1), 115-119
CODEN: JADID7; ISSN: 0165-0327

PUBLISHER: Elsevier Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Background: Selective serotonin (5-HT) and norepinephrine (NE) reuptake inhibitors (SNRIs) like duloxetine have the efficacy of tricyclic antidepressants (TCAs) with a more tolerable side-effect profile. Bipolar disorder is often undetected, with the most common misdiagnosis being unipolar depression. Studies have suggested that treatment of bipolar and unipolar depression with heterocyclic TCAs may increase the risk of switch rate to mania. Studies of antidepressants in unipolar major depression show a small risk of mania or hypomania, presumably because some bipolar depressives were mistakenly studied. This study investigated the rate of hypomania, mania, and hypomanic-like symptoms observed during treatment with duloxetine in patients with major depression. Methods: This was a retrospective anal. of data from eight placebo-controlled, double-blind, randomized clin. trials of duloxetine in patients with non-bipolar major depression. Limitations: The studies were of limited duration. Manic or hypomanic symptoms were not elicited using standardized mania rating scale instruments. Results: One case of mania occurred in the placebo group (0.1%), and two cases of hypomania were observed in the duloxetine-treated group (0.2%). Among hypomanic-like symptoms, only insomnia was significantly higher in the duloxetine group than in the placebo group ($p < 0.05$). Conclusions: Duloxetine was associated with a low incidence of treatment-emergent hypomania, mania, or hypomanic-like symptoms in patients with major depressive disorder (MDD). The low incidence reported here may be due to greater diagnostic diligence on the part of the investigators. It is possible that the cases reported likely reflect inclusion of misdiagnosed bipolar II patients rather than true unipolar MDD cases. The effect of duloxetine in patients with bipolar depression is not known.

CC 1-11 (Pharmacology)

IT **Mental disorder**

(major depression; duloxetine was associated with low incidence of treatment emergent hypomania, mania or hypomanic-like symptoms in major depression disorder patient)

IT **Mental disorder**

(mania; duloxetine was not significantly associated with mania in major depression disorder patient)

IT 116539-59-4, Duloxetine

RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological

activity); THU (Therapeutic use); BIOL (Biological study);
USES (Uses)

(duloxetine was associated with low incidence of treatment emergent
hypomania, mania or hypomanic-like symptoms in major depression
disorder patient)

REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 149 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2005:261672 HCAPLUS

DOCUMENT NUMBER: 142:475925

TITLE: A cost-effectiveness model of escitalopram,
citalopram, and venlafaxine as first-line treatment
for major depressive disorder in Belgium

AUTHOR(S): Demyttenaere, Koen; Hemels, Michiel E. H.; Hudry,
Joumana; Annemans, Lieven

CORPORATE SOURCE: Department of Psychiatry, University Hospital
Gasthuisberg, Louvain, Belg.

SOURCE: Clinical Therapeutics (2005), 27(1), 111-124
CODEN: CLTHDG; ISSN: 0149-2918

PUBLISHER: Excerpta Medica, Inc.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Background: Economic evaluations aim to combine costs and patient outcomes
in one anal. Objective: The purpose of this study was to assess the
cost-effectiveness of escitalopram (vs all available competitors) for
first-line treatment of major depressive disorder (MDD) in Belgium.
Methods: A 2-path decision analytic model with a 6-mo horizon was used.
All patients (baseline scores on the Montgomery-Asberg Depression Rating
Scale [MADRS], ≥ 18 to ≤ 40) started at the primary path, and
were referred to specialist care in the secondary care path. Model inputs
included the following: probabilities from a meta-anal. of comparative
trials data, an ad-hoc survey to evaluate pharmacol. treatment of
depression in Belgium, literature, and a panel of experts. Main outcome
measures were success (ie, remission [defined as MADRS ≤ 12]) and
costs of treatment (ie, drug costs and medical care). Analyses were
performed from the perspectives of the Belgian insurance system (IS) and
society. The friction-cost method was used to estimate costs of lost
productivity. Monetary values are reported in year-2003 euros (EU1.0
 \approx US \$1.1 in 2003). Results: The expected success rate was 62.3%
(95% CI, 60.1%-64.5%) for escitalopram compared with 57.2% (95% CI,
55.0%-59.4%) for citalopram. From the IS perspective, the expected cost
per patient was EU390 (95% CI, EU372-EU409) for escitalopram compared with
EU411 (95% CI, EU391-EU431) for citalopram. From the societal
perspective, these costs were EU1162 (95% CI, EU1106-EU1221) and EU1276
(95% CI, EU1216-EU1336), resp. The success rates of venlafaxine (66.6%
[95% CI, 64.2%-69.0%]) and escitalopram (67.0% [95% CI, 64.7%-69.4%]) were
similar, but higher total costs were observed with venlafaxine, due to
acquisition and secondary care costs. The use of data from various
sources may have introduced bias. However, sensitivity analyses
demonstrated that results of the model were robust. Conclusions: In this
anal., the treatment of MDD with escitalopram appeared to be a
cost-effective alternative compared with citalopram and venlafaxine,
leading to better clin. outcomes and cost savings compared with citalopram
in the model used. The success rates were similar between venlafaxine and
escitalopram, but higher total costs were observed with venlafaxine.

CC 1-11 (Pharmacology)

IT Mental disorder

(major depression; escitalopram was cost-effective with

better clin. outcomes than citalopram and venlafaxine in major depressive disorder patient in Belgium)

IT 59729-33-8, Citalopram 93413-69-5, Venlafaxine 128196-01-0, Escitalopram

RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study);

USES (Uses)

(escitalopram was cost-effective with better clin. outcomes than citalopram and venlafaxine in major depressive disorder patient in Belgium)

REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 150 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2005:152921 HCAPLUS

DOCUMENT NUMBER: 142:475862

TITLE: Short-term difference in mood with sibutramine versus placebo in obese patients with and without depression

AUTHOR(S): Elfhag, Kristina; Roessner, Stephan

CORPORATE SOURCE: Swed.

SOURCE: Therapy (2005), 2(1), 107-112

CODEN: THERCR

PUBLISHER: Future Drugs Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Background: Sibutramine is an anti-obesity satiety-enhancing drug which elicits its effect by inhibiting the reuptake of serotonin and noradrenaline. Objective: The aim of this study was to test the short-term effect on mood with sibutramine vs. placebo in obese patients with and without depressive features. Materials & methods: The participants consisted of 36 obese patients with a mean body mass index of 39 kg/m². Depressive features were measured with the Comprehensive Psychopathol. Rating Scale (CPRS). Sibutramine (15 mg) and placebo were administered daily in a cross-over design over 14-day periods. At baseline, 19 (53%) patients demonstrated depressive features. Results: A significant short-term difference, implying lower mood with sibutramine vs. placebo, was observed for depressed patients, in particular, in the CPRS subscale for anxiety. This result persisted as statistically significant also when removing an item on increased sleeping difficulties in the CPRS anxiety scale. Sleeping difficulties, which are common side effects of anti-obesity drugs, were also greater with sibutramine in depressed patients. No differences were found in the nondepressed population. Conclusion: Patients with depressive features can be more susceptible to experiencing a relatively higher initial discomfort with sibutramine compared with placebo at onset of treatment.

CC 1-11 (Pharmacology)

IT **Mental disorder**

(depression; short-term difference in mood with sibutramine vs. placebo in obese patients with and without depression)

IT 106650-56-0, Sibutramine

RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study);

USES (Uses)

(short-term difference in mood with sibutramine vs. placebo in obese patients with and without depression)

REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 151 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2004:921076 HCAPLUS
DOCUMENT NUMBER: 142:273796
TITLE: Trazodone addition for insomnia in
venlafaxine-treated, depressed inpatients: a
semi-naturalistic study
AUTHOR(S): Bertschy, Gilles; Ragama-Pardos, Emna; Muscionico,
Michel; Ait-Ameur, Abderrafi; Roth, Loraine; Osiek,
Christian; Ferrero, Francois
CORPORATE SOURCE: Department of Psychiatry, University Hospital and
University of Geneva, Geneva, Switz.
SOURCE: Pharmacological Research (2005), 51(1), 79-84
CODEN: PHMREP; ISSN: 1043-6618
PUBLISHER: Elsevier B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB In this paper, we present the results of a prospective semi-naturalistic
study of the addition of trazodone for insomnia to a 4 wk, 300 mg/day
venlafaxine treatment in 50 depressed inpatients. The Montgomery and
Asberg depression rating scale was used as a rating instrument. The study
is designated as semi-naturalistic due to the fact that, although the
venlafaxine treatment regimen was strictly defined, the timing of the
trazodone introduction and the dosage were determined by the clinicians. The
indication was based on the persistency of insomnia despite the use of
authorized sedative co-medication (zopiclone as a hypnotic, clorazepate as
an anxiolytic). Among the 42 patients who completed the study, 27 did not
receive trazodone (G1) while 15 did (G2). Although the two groups were
not clin. different at study entry, G2 patients showed less improvement
than G1 patients during venlafaxine treatment alone, both in terms of
insomnia (MADRS item 4) and inner tension (MADRS item 3). After trazodone
introduction, insomnia improved and the median (interquartile range) of
this item in G1 and G2 patients showed no statistically significant
difference on Day 28 (G1:0 (0-1); G2:0 (0-2)). However, inner tension did
not improve and the median (interquartile range) was higher on Day 28 in
G2 patients (G1: 1 (0-2); G2: 2(1-4); P < 0.05). Thus, trazodone is
probably used for patients who develop not only insomnia, but also inner
tension/anxiety during venlafaxine treatment. However, it alleviates only
the first symptom, not the second.
CC 1-11 (Pharmacology)
IT **Mental disorder**
(**depression**; trazodone improved hypnotic zopiclone-resistant
insomnia but not inner tension and anxiety associated with insomnia, was
well tolerated with no adverse effects in depressed high dose
venlafaxine treated patient)
IT **93413-69-5, Venlafaxine**
RL: **PAC (Pharmacological activity); THU (Therapeutic**
use); BIOL (Biological study); USES (Uses)
(trazodone improved venlafaxine induced zopiclone-resistant insomnia
but not inner tension and anxiety associated with insomnia, was well
tolerated with no adverse effects in **depressed** patient)
REFERENCE COUNT: 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 152 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2005:150603 HCAPLUS
DOCUMENT NUMBER: 142:456824
TITLE: The combined treatment of venlafaxine and ECT in
treatment-resistant depressive patients
AUTHOR(S): Dilbaz, Nesrin; Senguel, Cem; Okay, Tuncer; Bayam,
Goeksel; Tuerkoglu, Ali

CORPORATE SOURCE: Psychiatry clinic Samanpazari, Ankura Numune Research and Training Hospital II., Ankura, Turk.

SOURCE: International Journal of Psychiatry in Clinical Practice (2005), 9(1), 55-59
CODEN: IJPCFZ; ISSN: 1365-1501

PUBLISHER: Taylor & Francis

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Objective: To evaluate the efficacy and safety of the combination treatment of ECT and venlafaxine among treatment-resistant depressive patients. Methods: We reviewed 21 depressive patients who were treated with a combination of electroconvulsive therapy (ECT) and venlafaxine. The indication of the ECT-venlafaxine treatment was inadequate response to at least one antidepressant trial of adequate doses and duration. Propofol was used as an anesthetic agent during ECT treatments. Results: Ninety percent of the patients benefited from the combined treatment. The responsiveness to the combination treatment was not associated with high dose of venlafaxine. In most of the patients, the combined treatment was safe and well tolerated. Adverse reactions occurred in 57% of the patients and included concentration difficulties (four patients), memory problems (seven patients) and headache (one patient). No asystole was observed. Treatment was safe with a low dose of venlafaxine equal to or lower than 225 mg/day. Conclusions: It seems that treatment of ECT combined with low dose venlafaxine and propofol as anesthetic agent is effective and safe. This strategy may be a therapeutic option in treatment-resistant depressive patients.

CC 1-11 (Pharmacology)

IT **Mental disorder**
(**depression**; combination therapy of low dose venlafaxine, electroconvulsive therapy and anesthetic agent propofol was effective, well tolerated and safe in treatment-resistant depressive patient)

IT **93413-69-5, Venlafaxine**
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study);
USES (Uses)
(combination therapy with low dose venlafaxine, electroconvulsive therapy and anesthetic agent propofol was effective, well tolerated and safe in treatment-resistant depressive patient)

REFERENCE COUNT: 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 153 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2005:4621 HCAPLUS

DOCUMENT NUMBER: 142:329574

TITLE: Randomized double-blind comparison of serotonergic (Citalopram) versus noradrenergic (Reboxetine) reuptake inhibitors in outpatients with somatoform, DSM-IV-TR pain disorder

AUTHOR(S): Aragona, Massimiliano; Bancheri, Lara; Perinelli, Donatella; Tarsitani, Lorenzo; Pizzimenti, Alessia; Conte, Antonella; Inghilleri, Maurizio

CORPORATE SOURCE: Department of Psychiatry, University of Rome "La Sapienza", Rome, 30 00185, Italy

SOURCE: European Journal of Pain (Amsterdam, Netherlands) (2005), 9(1), 33-38
CODEN: EJPAFJ; ISSN: 1090-3801

PUBLISHER: Elsevier B.V.

DOCUMENT TYPE: Journal

LANGUAGE: English

- AB Whether the effect of tricyclic antidepressants on Pain Disorder arises from their noradrenergic or serotonergic actions or both remains unclear. We compared the selective serotonin reuptake inhibitor (SSRI) citalopram and the noradrenergic reuptake inhibitor (NARI) reboxetine in outpatients with Pain Disorder. We also distinguished the drugs' analgesic and antidepressant effects. In this 8-wk, randomized double-blind study, 35 patients with a DSM-IV-TR diagnosis of Pain Disorder were randomly assigned to receive either citalopram 40 mg/day (N=17 patients) or reboxetine 8 mg/day (N=18). The Present Pain Intensity (PPI) scale and the Total Pain Rating Index (tPRI) of the McGill Pain Questionnaire were used to measure the effect on pain symptoms. Changes in the Zung Self-Rating Depression Scale (Zung-D) scores were evaluated to monitor a possible antidepressant effect. For all patients who had at least one assessment, an intent-to-treat anal. was performed. No significant differences were found in the demog. variables or clin. characteristics of the two treatment groups. In the citalopram group, PPI and tPRI scores measured at baseline decreased after treatment (tPRI: 41.9 vs. 30.0, $p=.004$; PPI: 3.5 vs. 2.8, $p=.045$) whereas in the reboxetine group differences were not statistically significant (tPRI: 35.2 vs. 31.5; PPI: 3.7 vs. 3.1). The Zung-D showed no significant changes between baseline and endpoint assessment in either group. Our study suggests that the SSRI citalopram may have a moderate analgesic effect in patients with Pain Disorder, and that this analgesic activity appears to be not correlated to changes in depressive scores. If confirmed in a larger sample, this evidence suggests that patients who are intolerant or resistant to tricyclic antidepressants, may be treated with SSRIs.
- CC 1-11 (Pharmacology)
- ST citalopram reboxetine somatoform **pain** disorder analgesic antidepressant
- IT Pain
(citalopram but not noradrenergic reuptake inhibitor reboxetine is therapeutically effective in showing specific analgesic effect which is not dependent on **depressive** scores in outpatient with somatoform, DSM-IV-TR-**pain** disorder)
- IT Analgesics
(citalopram but not reboxetine is therapeutically effective in showing specific analgesic effect which is not dependent on **depressive** scores in outpatient with somatoform, DSM-IV-TR-**pain** disorder)
- IT Nervous system agents
(noradrenaline reuptake inhibitors; citalopram but not noradrenergic reuptake inhibitor reboxetine is therapeutically effective in showing specific analgesic effect which is not dependent on **depressive** scores in outpatient with somatoform, DSM-IV-TR-**pain** disorder)
- IT 5-HT reuptake inhibitors
(selective serotonin reuptake inhibitor citalopram but not reboxetine is effective in showing specific analgesic effect which is not dependent on **depressive** scores in outpatient with somatoform, DSM-IV-TR-**pain** disorder)
- IT Mental disorder
(somatoform disorder; citalopram but not noradrenergic reuptake inhibitor reboxetine is therapeutically effective in showing specific analgesic effect which is not dependent on **depressive** scores in outpatient with somatoform, DSM-IV-TR-**pain** disorder)
- IT Antidepressants
Human
(tricyclic antidepressant citalopram but not reboxetine is therapeutically effective in showing specific analgesic effect which is

not dependent on **depressive** scores in outpatient with
somatoform, DSM-IV-TR-**pain** disorder)

IT Antidepressants

(tricyclic; tricyclic antidepressant citalopram but not reboxetine is
therapeutically effective in showing specific analgesic effect which is
not dependent on **depressive** scores in outpatient with
somatoform, DSM-IV-TR-**pain** disorder)

IT 71620-89-8, Reboxetine

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL
(Biological study); USES (Uses)

(citalopram but not noradrenergic reuptake inhibitor reboxetine is
therapeutically effective in showing specific analgesic effect which is
not dependent on **depressive** scores in outpatient with
somatoform, DSM-IV-TR-**pain** disorder)

IT 59729-33-8, Citalopram

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL
(Biological study); USES (Uses)

(tricyclic antidepressant citalopram but not reboxetine is
therapeutically effective in showing specific analgesic effect which is
not dependent on **depressive** scores in outpatient with
somatoform, DSM-IV-TR-**pain** disorder)

REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 154 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2005:442684 HCAPLUS

DOCUMENT NUMBER: 143:186522

TITLE: Response period of combined fluvoxamine and
milnacipran treatment for depression

AUTHOR(S): Morishita, Shigeru; Arita, Seizaburo

CORPORATE SOURCE: Depression Prevention Medical Center, Kyoto Jujo
Hospital, Kyoto, 601-8325, Japan

SOURCE: International Medical Journal (2005), 12(1), 25-26
CODEN: IMJOFS; ISSN: 1341-2051

PUBLISHER: Japan International Cultural Exchange Foundation

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Objective: In providing drug treatment, it is important to appear the
faster onset of response to patients. Antidepressants typically take two
to four weeks to provide substantial benefit. The purpose of this clin.
practice was to determine the response period of combined fluvoxamine and
milnacipran treatment for depression. Design: Open clin. study. Methods:
Open clin. study was carried out among twenty-one depression patients.
They were receiving 50 mg of fluvoxamine and 50 mg of milnacipran to treat
depression. Results: The cumulative percentage of responder receiving
fluvoxamine and milnacipran reached over 80% after three weeks.

CC 1-11 (Pharmacology)

IT **Mental disorder**

(**depression**; response period of fluvoxamine and milnacipran
combined treatment for **depression**)

IT 54739-18-3, Fluvoxamine 92623-85-3, Milnacipran

RL: PAC (Pharmacological activity); THU (Therapeutic
use); BIOL (Biological study); USES (Uses)

(response period of fluvoxamine and milnacipran combined treatment for
depression)

REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 155 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2005:143853 HCAPLUS
DOCUMENT NUMBER: 142:348863
TITLE: Duloxetine in the treatment of major depressive disorder: a comparison of efficacy in patients with and without melancholic features
AUTHOR(S): Mallinckrodt, Craig H.; Watkin, John G.; Liu, Chaofeng; Wohlreich, Madelaine M.; Raskin, Joel
CORPORATE SOURCE: Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, IN, 46285, USA
SOURCE: BMC Psychiatry (2005), 5, No pp. given
CODEN: BPMSCU; ISSN: 1471-244X
URL: <http://www.biomedcentral.com/content/pdf/1471-244X-5-1.pdf>
PUBLISHER: BioMed Central Ltd.
DOCUMENT TYPE: Journal; (online computer file)
LANGUAGE: English

AB Background: The most prominent feature of melancholic depression is a near-total loss of the capacity to derive pleasure from activities or other pos. stimuli. Addnl. symptoms can include psychomotor disturbances, anorexia, excessive guilt, and early awakening from sleep. Melancholic patients may exhibit treatment responses and outcomes that differ from those of non-melancholic patients. Pooled data from double-blind, placebo-controlled studies were utilized to compare the efficacy of duloxetine in depressed patients with and without melancholic features. Methods: Efficacy data were pooled from 8 double-blind, placebo-controlled clin. trials of duloxetine. The presence of melancholic features (DSM-IV criteria) was determined using results from the Mini International Neuropsychiatric Interview (MINI). Patients (aged ≥ 18 years) meeting DSM-IV criteria for major depressive disorder (MDD) received duloxetine (40-120 mg/d; melancholic, N=759; non-melancholic, N=379) or placebo (melancholic, N=519; non-melancholic, N=256) for up to 9 wk. Efficacy measures included the 17-item Hamilton Rating Scale for Depression (HAM-D17) total score, HAM-D17 subscales (Maier, anxiety, retardation, sleep), the Clin. Global Impression of Severity (CGI-S) and Patient Global Impression of Improvement (PGI-I) scales, and Visual Analog Scales (VAS) for pain. Results: In data from all 8 studies, duloxetine's advantage over placebo did not differ significantly between melancholic and non-melancholic patients (treatment-by-melancholic status interactions were not statistically significant). Duloxetine demonstrated significantly greater improvement in depressive symptom severity, compared with placebo, within both melancholic and non-melancholic cohorts ($p \leq .001$ for HAM-D17 total score, CGI-S and PGI-I). When analyzed by gender, the magnitude of improvement in efficacy outcomes did not differ significantly between duloxetine-treated male and female melancholic patients. In the two studies that assessed duloxetine 60 mg once-daily dosing, duloxetine-treated melancholic patients had significantly greater improvement compared with placebo on HAM-D17 total score, CGI-S, PGI-I, 3 of 4 subscales of the HAM-D17, and VAS overall pain severity ($p < .01$). Estimated probabilities of response and remission were significantly greater for melancholic patients receiving duloxetine 60 mg QD compared with placebo (response 74.7% vs. 42.2%, resp., $p < .001$; remission 44.4% vs. 24.7%, resp., $p = .002$). Conclusions: In this anal. of pooled data, the efficacy of duloxetine in patients with melancholic features did not differ significantly from that observed in non-melancholic patients.

CC 1-11 (Pharmacology)

IT **Mental disorder**

(**depression**; duloxetine was effective in improving depressive symptom severity with improved HAM-D17, CGI-S, PGI-I, VAS overall pain severity and remission with no significant difference in gender,

melancholic and non-melancholic MDD patient)

IT **Mental disorder**

(major **depression**; duloxetine was effective in improving depressive symptom severity with improved HAMD17, CGI-S, PGI-I, VAS overall pain severity and remission with no significant difference in gender, melancholic and non-melancholic MDD patient)

IT **116539-59-4, Duloxetine**

RL: **PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)**

(duloxetine was effective in improving **depressive** symptom severity with improved HAMD17, CGI-S, PGI-I, VAS overall pain severity and remission with no significant difference in gender, melancholic and non-melancholic MDD patient)

REFERENCE COUNT: 57 THERE ARE 57 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 156 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2004:1156491 HCAPLUS

DOCUMENT NUMBER: 142:69208

TITLE: Gaboxadol and serotonin reuptake inhibitors for the treatment of depression and other affective disorders

INVENTOR(S): Sanchez, Connie; Ebert, Bjarke

PATENT ASSIGNEE(S): H. Lundbeck A/S, Den.

SOURCE: PCT Int. Appl., 26 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004112786	A2	20041229	WO 2004-DK459	20040625
WO 2004112786	A3	20050414		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

US 2005234093	A1	20051020	US 2004-20632	20041222
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PRIORITY APPLN. INFO.:

DK 2003-956	A	20030625
US 2003-483019P	P	20030625
DK 2004-16	A	20040107
US 2004-535123P	P	20040107
WO 2004-DK459	A2	20040625

AB The present invention relates to use of gaboxadol for preparing a pharmaceutical composition for treating depression. Moreover, it relates to the use of gaboxadol for the preparation of a pharmaceutical composition to be used

in combination with a serotonin reuptake inhibitor or any other compound, which causes an elevation in the level of extracellular serotonin.

IC ICM A61K031-437

ICS A61K031-445; A61K031-343; A61K031-4439; A61K031-404; A61K031-15;

A61P025-18

CC 1-11 (Pharmacology)

IT **Mental disorder**(affective; gaboxadol and serotonin reuptake inhibitors for treatment of **depression** and other affective disorders)IT **Mental disorder**(attention deficit hyperactivity disorder; gaboxadol and serotonin reuptake inhibitors for treatment of **depression** and other affective disorders)IT **Mental disorder**(cognitive; gaboxadol and serotonin reuptake inhibitors for treatment of **depression** and other affective disorders)IT **Mental disorder**(depression; gaboxadol and serotonin reuptake inhibitors for treatment of **depression** and other affective disorders)IT **Mental disorder**(impulse control disorder; gaboxadol and serotonin reuptake inhibitors for treatment of **depression** and other affective disorders)IT **Mental disorder**(neurotic **depression**; gaboxadol and serotonin reuptake inhibitors for treatment of **depression** and other affective disorders)IT **Mental disorder**(phobia; gaboxadol and serotonin reuptake inhibitors for treatment of **depression** and other affective disorders)

IT 50-49-7, Imipramine 303-49-1, Clomipramine 54739-18-3, Fluvoxamine 54910-89-3, Fluoxetine 59729-33-8, Citalopram 59859-58-4, Femoxetine 61869-08-7, Paroxetine 64603-91-4, Gaboxadol 65202-63-3 79617-96-2, Sertraline 83366-66-9, Nefazodone 85118-33-8, Gaboxadol hydrochloride 93413-69-5, Venlafaxine 116539-59-4, Duloxetine 119356-77-3, Dapoxetine 128196-01-0, Escitalopram 815574-58-4 815574-59-5 815574-59-5D, salts or hydrates 815574-60-8 815574-60-8D, salts or hydrates 815574-61-9 815574-61-9D, salts or hydrates 815574-62-0 815574-62-0D, salts or hydrates 815574-63-1 815574-63-1D, salts or hydrates 815574-64-2 815574-64-2D, salts or hydrates 815574-65-3 815574-65-3D, salts or hydrates 815574-66-4 815574-66-4D, salts or hydrates 815574-67-5 815574-67-5D, salts or hydrates 815574-68-6 815574-68-6D, salts or hydrates 815574-69-7 815574-69-7D, salts or hydrates 815574-70-0 815574-70-0D, salts or hydrates 815574-71-1 815574-71-1D, salts or hydrates

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(gaboxadol and serotonin reuptake inhibitors for treatment of **depression** and other affective disorders)

L91 ANSWER 157 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2004:799570 HCAPLUS

DOCUMENT NUMBER: 141:296026

TITLE: Preparation of biaryl substituted triazoles as sodium channel blockers

INVENTOR(S): Chakravarty, Prasun K.; Fisher, Michael H.; Palucki, Brenda; Park, Min K.; Parsons, William H.; Zhou, Bishan; Carey, James P.; Frantz, Douglas E.; Kress, Michael H.; Weaver, Damian

PATENT ASSIGNEE(S): Merck & Co., Inc., USA

SOURCE: PCT Int. Appl., 84 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
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WO 2004083189	A1	20040930	WO 2004-US7597	20040312
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2005119261	A1	20050602	US 2004-799230	20040312
PRIORITY APPLN. INFO.:			US 2003-455952P	P 20030318

OTHER SOURCE(S): MARPAT 141:296026

AB Title compds. I and II [wherein R1 = H, NO₂, (un)substituted (cyclo)alkyl, alkenyl, alkynyl, amino, ureido, carboxy, carbamoyl, heterocyclyl, etc.; R2 = H, (un)substituted (cyclo)alkyl, (hetero)aryl, carbamoyl, carboxy, etc.; R3, R4 = independently H, CN, NH₂, NO₂, halo, (un)substituted (cyclo)alkyl, alkenyl, alkynyl, alkoxy, (hetero)aryloxy, etc.; R5-R7 = independently H, CN, NH₂, NO₂, halo, (un)substituted (cyclo)alkyl, alkenyl, alkynyl, alkoxy, (hetero)aryloxy, ureido, carbamoyl, etc.; with provisos; and pharmaceutically acceptable salts thereof] were prepared as sodium channel blockers. For example, 2-(trifluoromethoxy)phenylboronic acid (preparation given) was coupled with Et 3-bromobenzoate, and the resulting biphenylcarboxylate saponified and amidated to give 3-(2-trifluoromethoxyphenyl)benzamide. Reaction of the amide with N,N-dimethylformamide di-Me acetal, followed by heating with NH₂NH₂•H₂O provided the triazole III. Compds. of the invention displayed sodium channel blocking activity against HEK cells stably transfected with PN1 Na channels from about <0.1 mM to about <50 mM by causing cell depolarization when sodium ions permeated through the agonist-modified channels. Pharmaceutical compns. comprising I or II, either alone or in combination with one or more other therapeutically active compds., are useful for treating conditions associated with or caused by Na channel activity, including acute pain, chronic pain, visceral pain, inflammatory pain, neuropathic pain, epilepsy, irritable bowel syndrome, depression, anxiety, multiple sclerosis, and bipolar disorder (no data).

IC ICM C07D249-08

ICS C07D249-10; A61K031-4196; A61P025-00

CC 28-10 (Heterocyclic Compounds (More Than One Hetero Atom))

Section cross-reference(s): 1, 63

IT Nervous system agents

(noradrenaline reuptake inhibitors,

combination therapy; preparation of biaryl substituted triazoles as sodium channel blockers)

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 158 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2004:696373 HCAPLUS

DOCUMENT NUMBER: 141:225723

TITLE: Preparation of 8-azabicyclo[3.2.1]octane derivatives

for use in pharmaceutical compositions as monoamine neurotransmitter reuptake inhibitors

INVENTOR(S): Peters, Dan; Nielsen, Elsebet Ostergaard; Olsen, Gunnar M.; Scheel-Krueger, Jorgen

PATENT ASSIGNEE(S): Neurosearch A/S, Den.

SOURCE: PCT Int. Appl., 33 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004072071	A1	20040826	WO 2004-EP50107	20040210
W:	AE, AE, AG, AL, AL, AM, AM, AM, AT, AT, AU, AZ, AZ, BA, BB, BG, BG, BR, BR, BW, BY, BY, BZ, BZ, CA, CH, CN, CN, CO, CO, CR, CR, CU, CU, CZ, CZ, DE, DE, DK, DK, DM, DZ, EC, EC, EE, EE, EG, ES, ES, FI, FI, GB, GD, GE, GE, GH, GM, HR, HR, HU, HU, ID, IL, IN, IS, JP, JP, KE, KE, KG, KG, KP, KP, KR, KR, KZ, KZ, LC, LK, LR, LS, LS, LT, LU, LV, MA, MD, MD, MG, MK, MN, MW, MX, MX, MZ, MZ, NA, NI			
RW:	BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG			
CA 2515584	AA	20040826	CA 2004-2515584	20040210
PRIORITY APPLN. INFO.:			DK 2003-213	A 20030212
			US 2003-448106P	P 20030220
			WO 2004-EP50107	W 20040210

OTHER SOURCE(S): MARPAT 141:225723

AB This invention relates to novel 8-azabicyclo[3.2.1]octane derivs., such as I [R = H, alkyl; R2 = CH2ORa, CH2SRa; R3 = substituted- or unsubstituted-heteroaryl; Ra = substituted- or unsubstituted-Ph or -naphthyl], useful as monoamine neurotransmitter re-uptake inhibitors. These 8-azabicyclo[3.2.1]octanes are claimed for use in the treatment of mood disorder, depression, atypical depression, major depressive disorder, dysthymic disorder, bipolar disorder, bipolar I disorder, bipolar II disorder, cyclothymic disorder, mood disorder due to a general medical condition, substance-induced mood disorder, pseudodementia, Ganser's syndrome, obsessive compulsive disorder, panic disorder, panic disorder without agoraphobia, panic disorder with agoraphobia, agoraphobia without history of panic disorder, panic attack, memory deficits, memory loss, attention deficit hyperactivity disorder, obesity, anxiety, generalized anxiety disorder, eating disorder, Parkinson's disease, dementia, dementia of ageing, senile dementia, Alzheimer's disease, acquired immunodeficiency syndrome dementia complex, memory dysfunction in ageing, specific phobia, social phobia, posttraumatic stress disorder, acute stress disorder, drug addiction, drug misuse, cocaine abuse, nicotine abuse, tobacco abuse, alc. addiction, alcoholism, pain, inflammatory pain, neuropathic pain, migraine pain, tension-type headache, chronic tension-type headache and **pain associated with depression**. Further, these compds. are claimed for use in the treatment of , fibromyalgia, arthritis, osteoarthritis, rheumatoid arthritis, back pain, cancer pain, irritable bowel pain, irritable bowel syndrome, postoperative pain, post-stroke pain, drug-induced neuropathy, diabetic neuropathy, sympathetically-maintained pain, trigeminal neuralgia, dental pain, myofacial pain, phantom-limb pain, bulimia, premenstrual syndrome, late luteal phase

syndrome, posttraumatic syndrome, chronic fatigue syndrome, urinary incontinence, stress incontinence, urge incontinence, nocturnal incontinence, premature ejaculation, erectile difficulty, anorexia nervosa, sleep disorders, autism, mutism, trichotillomania, narcolepsy, post-stroke depression, stroke-induced brain damage, stroke-induced neuronal damage or Gilles de la Tourette disease. In other aspects the invention relates to the use of these compds. in a method for therapy and to pharmaceutical compns. comprising the compds. of the invention. Thus, the tropane derivative, (2R,3S)-2-(2,3-dichlorophenoxyethyl)-8-methyl-3-(2-thienyl)-1-azabicyclo[3.2.1]octane (II), was prepared via a series of synthetic steps starting from (+)-2-carbomethoxytropinone, 2-thienylmagnesium bromide, and 2,3-dichlorophenol. The prepared 8-azabicyclo[3.2.1]octanes were tested for their ability to inhibit the reuptake of dopamine, noradrenaline and serotonin monoamine neurotransmitters in synaptosomes.

IC ICM C07D451-02

ICS A61K031-46; A61P025-00

CC 31-3 (Alkaloids)

Section cross-reference(s): 1, 63

IT **Nervous system agents**

(noradrenaline reuptake inhibitors;

preparation of 8-azabicyclo[3.2.1]octane derivs. for use in pharmaceutical compns. as monoamine neurotransmitter reuptake inhibitors)

L91 ANSWER 159 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2004:428895 HCAPLUS

DOCUMENT NUMBER: 140:423467

TITLE: Preparation of 3-aryloxy/thio-2,3-substituted
propanamines and their use in **inhibiting
serotonin and norepinephrine
reuptake**INVENTOR(S): Boulet, Serge Louis; Filla, Sandra Ann; Gallagher,
Peter Thaddeus; Hudziak, Kevin John; Johansson, Anette
Margareta; Karanjawala, Rushad E.; Masters, John
Joseph; Matassa, Victor; Mathes, Brian Michael;
Rathmell, Richard Edmund; Whatton, Maria Ann; Wolfe,
Chad Nolan

PATENT ASSIGNEE(S): Eli Lilly and Company, USA

SOURCE: PCT Int. Appl., 111 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004043904	A1	20040527	WO 2003-US31514	20031024
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW			
RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG			
EP 1587782	A1	20051026	EP 2003-777544	20031024

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK

PRIORITY APPLN. INFO.:

US 2002-424117P P 20021105

WO 2003-US31514 W 20031024

OTHER SOURCE(S): MARPAT 140:423467

- AB Title compds. I [A = O, S; X = (un)substituted Ph, thienyl; Y = Ph, naphthyl, dihydrobenzothienyl, benzothiazolyl, benzoisothiazolyl, quinolyl, etc.; Z = alkoxy, F; R1-2 = H, alkyl] are prepared For instance, 1-(benzylmethylamino)-5-methylhexan-3-ol (preparation given) is coupled to 4-hydroxybenzothiophene (PhMe, 1,1'-(azodicarbonyl)dipiperidine, Bu3P, 70°, 18 h) and the product debenzylated (1,2-dichloroethane, 1-chloroethyl chloroformate, reflux, 30 min) to give II. All example compds. have Ki < 100 nM at the serotonin transporter and norepinephrine transporter. I are useful for the treatment of, e.g., **depression**, **OCD**, **anxiety** and **pain**.
- IC ICM C07C217-64
ICS C07D333-56; A61P025-24; A61P025-18; A61P025-06; A61K031-381; A61K031-137
- CC 25-4 (Benzene, Its Derivatives, and Condensed Benzenoid Compounds)
Section cross-reference(s): 1, 63
- ST aryloxy thio substituted propanamine **inhibiting serotonin norepinephrine reuptake** prepn
- IT Mental disorder
(attention deficit hyperactivity disorder; preparation of 3-aryloxy/thio-2,3-substituted propanamines and their use in **inhibiting serotonin and norepinephrine reuptake**)
- IT Tobacco smoke
(cessation; preparation of 3-aryloxy/thio-2,3-substituted propanamines and their use in **inhibiting serotonin and norepinephrine reuptake**)
- IT Mental disorder
(depression; preparation of 3-aryloxy/thio-2,3-substituted propanamines and their use in **inhibiting serotonin and norepinephrine reuptake**)
- IT Menopause
(disorder, hot flash; preparation of 3-aryloxy/thio-2,3-substituted propanamines and their use in **inhibiting serotonin and norepinephrine reuptake**)
- IT Bladder, disease
(incontinence; preparation of 3-aryloxy/thio-2,3-substituted propanamines and their use in **inhibiting serotonin and norepinephrine reuptake**)
- IT Adrenoceptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(noradrenergic; preparation of 3-aryloxy/thio-2,3-substituted propanamines and their use in **inhibiting serotonin and norepinephrine reuptake**)
- IT Mental disorder
(obsession-compulsion; preparation of 3-aryloxy/thio-2,3-substituted propanamines and their use in **inhibiting serotonin and norepinephrine reuptake**)
- IT 5-HT reuptake inhibitors
Alcoholism
Amnesia
Analgesics
Antidepressants
Antiobesity agents
Anxiety

Anxiolytics

Human

Obesity

Pain

(preparation of 3-aryloxy/thio-2,3-substituted propanamines and their use in **inhibiting serotonin and norepinephrine reuptake**)

IT Biological transport

(reuptake; preparation of 3-aryloxy/thio-2,3-substituted propanamines and their use in **inhibiting serotonin and norepinephrine reuptake**)

IT 50-67-9, Serotonin, biological studies 51-41-2, Norepinephrine
330597-62-1, Cytochrome CYP2D6

RL: BSU (Biological study, unclassified); BIOL (Biological study)

(preparation of 3-aryloxy/thio-2,3-substituted propanamines and their use in **inhibiting serotonin and norepinephrine reuptake**)

IT 693257-96-4P, [3-((Benzo[b]thiophen-4-yl)oxy)-4-methylpentyl]methylaniline
693257-97-5P, [3-((Benzo[b]thiophen-4-yl)oxy)heptyl]methylaniline
693257-98-6P, [3-((Benzo[b]thiophen-4-yl)oxy)hexyl]methylaniline
693257-99-7P, [3-((Benzo[b]thiophen-4-yl)oxy)-4-cyclohexylbutyl]methylaniline

RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)

(preparation of 3-aryloxy/thio-2,3-substituted propanamines and their use in **inhibiting serotonin and norepinephrine reuptake**)

IT 693257-95-3P, [3-((Benzo[b]thiophen-4-yl)oxy)-5-methylhexyl]methylaniline
693258-01-4P, (R)-3-((Benzo[b]thiophen-4-yl)oxy)-4-cyclohexyl-N-methylbutan-1-amine hydrochloride 693258-02-5P, (S)-3-((Benzo[b]thiophen-4-yl)oxy)-4-cyclohexyl-N-methylbutan-1-amine hydrochloride 693258-03-6P, [(R)-3-((Benzo[b]thiophen-4-yl)oxy)-4-methylpentan-1-yl]methylaniline hydrochloride 693258-04-7P, [(S)-3-((Benzo[b]thiophen-4-yl)oxy)-4-methylpentan-1-yl]methylaniline hydrochloride 693258-05-8P, (R)-3-((Benzo[b]thiophen-4-yl)oxy)-N-methylhexan-1-amine hydrochloride 693258-06-9P, (S)-3-((Benzo[b]thiophen-4-yl)oxy)-N-methylhexan-1-amine hydrochloride 693258-07-0P, (R)-3-((Benzo[b]thiophen-4-yl)oxy)-N-methylheptan-1-amine hydrochloride 693258-08-1P, (S)-3-((Benzo[b]thiophen-4-yl)oxy)-N-methylheptan-1-amine hydrochloride 693258-09-2P, (2S,3S)-3-(3,5-Dichlorophenoxy)-1-methylaminohexan-2-ol hydrochloride 693258-11-6P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of 3-aryloxy/thio-2,3-substituted propanamines and their use in **inhibiting serotonin and norepinephrine reuptake**)

IT 78-95-5, 1-Chloro-2-propanone 79-44-7, N,N-Dimethylcarbonyl chloride
103-67-3, N-Benzylmethylaniline 107-14-2, Chloroacetonitrile 107-21-1,
1,2-Ethanediol, reactions 141-82-2, Malonic acid, reactions 394-50-3,
3-Fluoro-2-hydroxybenzaldehyde 452-08-4, 2-Bromo-4-fluoroanisole
459-60-9, 4-Fluoroanisole 591-35-5, 3,5-Dichlorophenol 673-22-3,
2-Hydroxy-4-methoxybenzaldehyde 758-16-7, N,N-Dimethylthioformamide
928-95-0, trans-2-Hexen-1-ol 1068-55-9, Isopropylmagnesium chloride
2032-35-1, Bromoacetaldehyde diethyl acetal 2234-82-4, Propylmagnesium
chloride 2365-48-2, Methyl thioglycolate 2439-68-1,
5-Benzyloxy-1-methyl-1H-indole 2550-36-9, Bromomethylcyclohexane
5464-79-9, 2-Amino-4-methoxybenzothiazole 5674-02-2, Isobutylmagnesium

chloride 7168-85-6, 7-Methoxybenzofuran 7217-59-6,
 2-Methoxybenzenethiol 7507-86-0, 2-Bromo-5-methoxybenzaldehyde
 7616-94-6, Perchloryl fluoride 13414-95-4, 6,7-Dihydro-1-benzothiophen-
 4(5H)-one 19158-51-1, Tosyl cyanide 19415-51-1, 5-Fluoro-2-
 methoxybenzaldehyde 20289-27-4, 7-Benzyloxy-1H-indole 88791-12-2,
 4-Bromo-7-methoxybenzo[b]thiophene 105728-90-3, 2-Fluoro-5-
 methoxybenzaldehyde 115144-40-6, 3,4-Difluoroanisole 128562-58-3,
 3-Bromo-N-methoxy-N-methylpropionamide 137654-20-7, 2-Fluoro-3-
 methoxybenzoic acid 146137-74-8, 2-Fluoro-6-methoxybenzaldehyde
 147460-41-1, 2-Bromo-5-fluorophenol 187543-87-9, 2,3-Difluoro-6-
 methoxybenzaldehyde 324769-10-0, 7-Bromo-6-fluorobenzothiophene
 476199-14-1, 4-Methoxybenzothiophene-2-carboxylic acid 476199-33-4,
 7-Benzyloxymethyl-1H-indole 693257-84-0, N-[2-
 (Methoxymethylcarbonyl)ethyl]-N-methylcarbamic acid tert-butyl ester
 693258-00-3, [3-((Benzo[b]thiophen-4-yl)oxy)-4-
 cyclohexylbutyl]methylcarbamic acid tert-butyl ester
 RL: RCT (Reactant); RACT (Reactant or reagent)

(preparation of 3-aryloxy/thio-2,3-substituted propanamines and their use in
 inhibiting serotonin and norepinephrine
 reuptake)

IT 450-88-4P, 2-Bromo-5-fluoroanisole 2513-49-7P, 5-Bromo-6,7-dihydro-1-
 benzothiophen-4(5H)-one 3048-46-2P, 4-Methoxybenzothiazole 3610-02-4P,
 Benzothiophen-4-ol 4790-81-2P, Benzofuran-7-ol 7405-23-4P,
 4-Hydroxybenzothiazole 7651-82-3P, Isoquinolin-6-ol 13523-92-7P,
 1-Methyl-1H-indol-5-ol 32373-06-1P, 1-(Benzylmethylamino)hexan-3-one
 35272-30-1P, 4-Methoxybenzo[d]isothiazole 52986-70-6P,
 6-Methoxyisoquinoline 56724-09-5P, 5-Methoxy-2-methylbenzaldehyde
 59845-54-4P, 4-Methylbenzothiophen-7-ol 67982-15-4P,
 Benzo[d]isothiazol-4-ol 74266-68-5P, 3-Fluoro-2-methoxybenzaldehyde
 77898-35-2P, Benzothiophen-7-ol 88791-08-6P, Benzothiophen-7-yl methyl
 ether 88791-18-8P, 7-Methoxybenzothiophene-2-carbonitrile 88791-26-8P,
 7-Methoxybenzo[d]isothiazole 92014-05-6P, 6-Methoxybenzothiophene-2-
 carbonitrile 92418-71-8P 94019-87-1P, 4-Cyano-7-hydroxybenzothiophene
 96803-64-4P, 1-[(2,2-Diethoxyethyl)thio]-2-methoxybenzene 98015-07-7P,
 4-Bromo-3-(1,3-dioxolan-2-yl)phenyl methyl ether 103438-88-6P,
 2-Fluoro-3-methoxybenzaldehyde 147317-39-3P, Benzo[d]isothiazol-7-ol
 170282-84-5P, 3-(1,3-Dioxolan-2-yl)-4-methylphenyl methyl ether
 217099-77-9P, 6-Hydroxybenzothiophene-2-carbonitrile 398456-80-9P,
 4-Fluoro-2-methoxybenzenethiol 446873-57-0P, 5-(2-Fluoro-5-
 methoxybenzylidene)-2-thioxo-1,3-thiazolidin-4-one 475577-33-4P,
 1-Methyl-1H-indol-7-ol 475577-34-5P, 7-Benzyloxy-1-methyl-1H-indole
 476198-74-0P, 3-Methoxy-5-trifluoromethylbenzenethiol 476198-75-1P,
 1-[(5-Fluoro-2-methoxyphenyl)thio]-2-propanone 476198-76-2P,
 1-[(2-Fluoro-5-methoxyphenyl)thio]-2-propanone 476198-77-3P,
 1-[(2,2-Diethoxyethyl)thio]-4-fluoro-2-methoxybenzene 476198-78-4P,
 1-[(2,2-Diethoxyethyl)thio]-3-methoxy-5-trifluoromethylbenzene
 476198-79-5P, 5-Fluorobenzothiophen-7-yl methyl ether 476198-80-8P,
 4-Trifluoromethylbenzothiophen-6-yl methyl ether 476198-81-9P,
 4-Fluoro-7-methoxybenzothiophene 476198-84-2P, 5-(3-Fluoro-2-
 methoxybenzylidene)-2-thioxo-1,3-thiazolidin-4-one 476198-86-4P,
 5-(2-Methyl-5-methoxybenzylidene)-2-thioxo-1,3-thiazolidin-4-one
 476198-88-6P, (Z)-3-(2-Fluoro-5-methoxyphenyl)-2-mercapto-2-propenoic acid
 476198-90-0P, (Z)-3-(3-Fluoro-2-methoxyphenyl)-2-mercapto-2-propenoic acid
 476198-91-1P, (Z)-3-(2-Methyl-5-methoxyphenyl)-2-mercapto-2-propenoic acid
 476198-92-2P, 4-Fluoro-7-methoxybenzothiophene-2-carboxylic acid
 476198-93-3P, 4-Methyl-7-methoxybenzothiophene-2-carboxylic acid
 476198-95-5P, 4-Methyl-7-methoxybenzothiophene 476198-96-6P,
 5-Fluoro-4-methoxybenzothiophene 476198-97-7P, 5-Fluoro-4-
 methoxybenzothiophene-2-carboxylic acid 476198-98-8P,

7-Fluoro-4-methoxybenzothiophene 476198-99-9P, 2-(5-Fluoro-2-methoxyphenyl)-2-hydroxy-N,N-dimethylethanethioamide 476199-00-5P, (7-Fluoro-4-methoxybenzothiophen-2-yl)dimethylamine 476199-01-6P, 7-Fluoro-4-methoxybenzothiophen-2(3H)-one 476199-02-7P, Methyl 7-fluoro-4-methoxybenzothiophene-2-carboxylate 476199-03-8P, 7-Fluoro-4-methoxybenzothiophene-2-carboxylic acid 476199-04-9P, 3-Chloro-4-fluoro-7-methoxybenzothiophene 476199-05-0P, (E)-3-(2-Fluoro-5-methoxyphenyl)-2-propenoic acid 476199-06-1P, Methyl 3-chloro-4-fluoro-7-methoxybenzothiophene-2-carboxylate 476199-07-2P, 3-Chloro-4-fluoro-7-methoxybenzothiophene-2-carboxylic acid 476199-08-3P, 4-Fluoro-7-methoxy-3-methylbenzothiophene 476199-09-4P, 7-Fluoro-4-methoxy-3-methylbenzothiophene 476199-10-7P, 2-Fluoro-7-methoxybenzothiophene 476199-11-8P, 2-Fluoro-4-methoxybenzothiophene 476199-12-9P, 2-Iodo-7-methoxybenzothiophene 476199-13-0P, 4-Methoxybenzothiophene-2-carbonitrile 476199-15-2P, 4-Fluoro-7-methoxybenzothiophene-2-carbonitrile 476199-16-3P, 4-Fluoro-7-methoxybenzothiophene-2-carboxamide 476199-17-4P, 4-Cyano-7-methoxybenzo[b]thiophene 476199-18-5P, O-(2-Formyl-5-methoxyphenyl) dimethylthiocarbamate 476199-19-6P, S-(2-Formyl-5-methoxyphenyl) dimethylthiocarbamate 476199-20-9P, 5-Fluorobenzothiophen-7-ol 476199-21-0P, 4-Trifluoromethylbenzothiophen-6-ol 476199-22-1P, 5-Fluorobenzo[b]thiophen-4-ol 476199-23-2P, 7-Fluorobenzothiophen-4-ol 476199-24-3P, 3-Chloro-4-fluorobenzothiophen-7-ol 476199-25-4P, 3-Methyl-4-fluorobenzothiophen-7-ol 476199-26-5P, 7-Fluoro-3-methylbenzothiophen-4-ol 476199-27-6P, 2-Fluorobenzothiophen-7-ol 476199-28-7P, 2-Fluorobenzothiophen-4-ol 476199-29-8P, 7-Hydroxybenzothiophene-2-carbonitrile 476199-30-1P, 4-Hydroxybenzothiophene-2-carbonitrile 476199-31-2P, 4-Fluoro-7-hydroxybenzothiophene-2-carbonitrile 476199-32-3P, 6-Fluorobenzothiophen-7-ol 507477-13-6P, 5-Fluoro-6,7-dihydro-5H-benzo[b]thiophen-4-one 693220-39-2P, 5-Bromo-5-fluoro-6,7-dihydro-5H-benzo[b]thiophen-4-one 693220-44-9P, 7-Methylbenzo[d]isothiazol-4-ol 693220-45-0P, 7-Bromo-4-methoxybenzo[d]isothiazole 693220-46-1P, 4-Methoxy-7-methylbenzo[d]isothiazole 693220-47-2P, 2-Fluoro-3-methoxy-N-methyl-N-methoxybenzamide 693220-48-3P, 4-Fluoro-2,3-dihydrobenzo[b]thiophen-7-ol 693220-49-4P, 4-Fluoro-7-methoxy-2,3-dihydrobenzo[b]thiophene 693220-90-5P, (2R,3S)-3-(3,5-Dichlorophenoxy)hexane-1,2-diol 693220-91-6P, (2R,3S)-3-(2,4-Dichlorophenoxy)hexane-1,2-diol 693220-92-7P, Toluene-4-sulfonic acid (2S,3S)-3-(3,5-dichlorophenoxy)-2-hydroxyhexyl ester 693220-93-8P, Toluene-4-sulfonic acid (2S,3S)-3-(2,4-dichlorophenoxy)-2-hydroxyhexyl ester 693257-81-7P, 3-(Benzylmethylamino)-N-methoxy-N-methylpropionamide 693257-82-8P, 1-(Benzylmethylamino)heptan-3-one 693257-83-9P, (4-Cyclohexyl-3-oxobutyl)methylcarbamic acid tert-butyl ester 693257-85-1P, 1-(Benzylmethylamino)heptan-3-ol 693257-86-2P, 1-(Benzylmethylamino)hexan-3-ol 693257-87-3P, N-(4-Cyclohexyl-3-hydroxybutyl)-N-methylcarbamic acid tert-butyl ester 693257-88-4P, 1-(N-Benzyl-N-methylamino)-5-methylhexan-3-ol 693257-89-5P, 1-(N-Benzyl-N-methylamino)-4-methylpentan-3-ol 693257-90-8P, [3-((Benzo[b]thiophen-4-yl)oxy)-5-methylhexyl]benzylmethylamine 693257-91-9P, [3-((Benzo[b]thiophen-4-yl)oxy)-4-methylpentyl]benzylmethylamine 693257-92-0P, [3-((Benzo[b]thiophen-4-yl)oxy)heptyl]benzylmethylamine 693257-93-1P, [3-((Benzo[b]thiophen-4-yl)oxy)hexyl]benzylmethylamine 693257-94-2P, N-[3-((Benzo[b]thiophen-4-yl)oxy)-4-(cyclohexyl)butyl]-N-methylcarbamic acid tert-butyl ester

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(preparation of 3-aryloxy/thio-2,3-substituted propanamines and their use in inhibiting serotonin and norepinephrine)

reuptake)

REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 160 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN
 ACCESSION NUMBER: 2004:428894 HCAPLUS
 DOCUMENT NUMBER: 140:423466
 TITLE: Preparation of 3-aryloxy/thio-2,3-substituted
 propanamines and their use in **inhibiting
 serotonin and norepinephrine
 reuptake**
 INVENTOR(S): Boulet, Serge Louis; Filla, Sandra Ann; Gallagher,
 Peter Thaddeus; Hudziak, Kevin John; Johansson, Anette
 Margareta; Karanjawala, Rushad E.; Masters, John
 Joseph; Matassa, Victor; Mathes, Brian Michael;
 Rathmell, Richard Edmund; Whatton, Maria Ann; Wolfe,
 Chad Nolan
 PATENT ASSIGNEE(S): Eli Lilly and Company, USA
 SOURCE: PCT Int. Appl., 164 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004043903	A1	20040527	WO 2003-US31513	20031024
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW			
RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG			
EP 1587781	A1	20051026	EP 2003-777543	20031024
R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK			
PRIORITY APPLN. INFO.:			US 2002-424176P	P 20021105
			WO 2003-US31513	W 20031024

OTHER SOURCE(S): MARPAT 140:423466

AB Title compds. I [A = O, S; X = (un)substituted Ph, thienyl; Y = Ph, naphthyl, dihydrobenzothienyl, benzothiazolyl, benzoisothiazolyl, quinolyl, etc.; Z = alkoxy, F; R1-2 = H, alkyl] are prepared For instance, (2R,3R)-3-phenylglycidol is treated with 1-naphthol (THF/H2O, NaOH, 75°, 4 h) to give (2R,3S)-3-(naphthalen-1-yloxy)-3-phenylpropane-1,2-diol. This intermediate is converted to the mesylate (CH2Cl2, pyridine, 10°, MsCl), treated with NaN3 (DMF, 65°, 5 h), fluorinated (CH2Cl2, DMAP, DeOxo-Fluor) and reduced (THF, PPh3) to give II. All example compds. have Ki < 100 nM at the serotonin transporter and norepinephrine transporter. I are useful for the treatment of, e.g., **depression, OCD, anxiety and pain.**

IC ICM C07C217-62

ICS C07C217-64; C07C323-32; C07D275-04; C07D307-86; C07D333-54;
 C07D333-56; A61K031-381; A61K031-137; A61K031-343; A61K031-425;
 A61P025-06; A61P025-18; A61P025-24

- CC 25-4 (Benzene, Its Derivatives, and Condensed Benzenoid Compounds)
Section cross-reference(s): 1, 63
- IT Mental disorder
(attention deficit hyperactivity disorder; preparation of 3-aryloxy/thio-2,3-substituted propanamines and their use in **inhibiting serotonin and norepinephrine reuptake**)
- IT Mental disorder
(depression; preparation of 3-aryloxy/thio-2,3-substituted propanamines and their use in **inhibiting serotonin and norepinephrine reuptake**)
- IT Menopause
(disorder, hot flash; preparation of 3-aryloxy/thio-2,3-substituted propanamines and their use in **inhibiting serotonin and norepinephrine reuptake**)
- IT Behavior
(disorder; preparation of 3-aryloxy/thio-2,3-substituted propanamines and their use in **inhibiting serotonin and norepinephrine reuptake**)
- IT Bladder, disease
(incontinence; preparation of 3-aryloxy/thio-2,3-substituted propanamines and their use in **inhibiting serotonin and norepinephrine reuptake**)
- IT 5-HT reuptake inhibitors
Alcoholism
Amnesia
Analgesics
Antidepressants
Antiobesity agents
Anxiety
Anxiolytics
Human
Obesity
Pain
(preparation of 3-aryloxy/thio-2,3-substituted propanamines and their use in **inhibiting serotonin and norepinephrine reuptake**)
- IT Biological transport
(reuptake; preparation of 3-aryloxy/thio-2,3-substituted propanamines and their use in **inhibiting serotonin and norepinephrine reuptake**)
- IT 50-67-9, Serotonin, biological studies 51-41-2, Norepinephrine
330597-62-1, Cytochrome CYP2D6
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(preparation of 3-aryloxy/thio-2,3-substituted propanamines and their use in **inhibiting serotonin and norepinephrine reuptake**)
- IT 693220-94-9P, (2S,3S)-2-Fluoro-3-(naphthalen-1-yloxy)-3-phenylpropylamine
693221-05-5P, [(2S,3S)-2-Fluoro-3-(naphthalen-1-yloxy)-3-phenylpropyl]dimethylamine 693221-60-2P, (2S,3S)-3-(Benzothiophen-4-yloxy)-2-fluoro-3-(3-fluorophenyl)propylamine 693221-61-3P, [(2S,3S)-3-(Benzothiophen-4-yloxy)-2-fluoro-3-(3-fluorophenyl)propyl]dimethylamine
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(preparation of 3-aryloxy/thio-2,3-substituted propanamines and their use in **inhibiting serotonin and norepinephrine reuptake**)

IT 693220-95-0P, (2R,3R)-2-Fluoro-3-(naphthalen-1-yloxy)-3-phenylpropylamine
693220-96-1P, (2S,3S)-3-(Benzofuran-7-yloxy)-2-fluoro-3-phenylpropylamine
693220-97-2P, (2S,3R)-3-(Benzothiophen-4-yloxy)-2-fluoro-3-phenylpropylamine
693220-98-3P, (2S,3S)-3-(Benzothiophen-4-yloxy)-2-fluoro-3-phenylpropylamine
693220-99-4P, (2R,3R)-3-(Benzothiophen-4-yloxy)-2-fluoro-3-phenylpropylamine
693221-00-0P, (2R,3S)-3-(Benzothiophen-4-yloxy)-2-fluoro-3-phenylpropylamine
693221-01-1P, (2R,3R)-3-(Benzofuran-7-yloxy)-2-fluoro-3-phenylpropylamine
693221-02-2P, (2S,3S)-3-(2-Methylbenzofuran-7-yloxy)-2-fluoro-3-phenylpropylamine
693221-03-3P, (2R,3S)-3-(Benzofuran-7-yloxy)-2-fluoro-3-phenylpropylamine
693221-04-4P, (2S,3S)-2-Fluoro-3-(5-fluorobenzothiophen-4-yloxy)-3-(3-fluorophenyl)propylamine
693221-06-6P, [(2R,3R)-2-Fluoro-3-(naphthalen-1-yloxy)-3-phenylpropyl]dimethylamine
693221-07-7P, [(2S,3S)-3-(Benzofuran-7-yloxy)-2-fluoro-3-phenylpropyl]dimethylamine
693221-08-8P, [(2S,3R)-3-(Benzothiophen-4-yloxy)-2-fluoro-3-phenylpropyl]dimethylamine
693221-09-9P, [(2S,3S)-3-(Benzothiophen-4-yloxy)-2-fluoro-3-phenylpropyl]dimethylamine
693221-10-2P, [(2R,3R)-3-(Benzothiophen-4-yloxy)-2-fluoro-3-phenylpropyl]dimethylamine
693221-11-3P, [(2R,3S)-3-(Benzothiophen-4-yloxy)-2-fluoro-3-phenylpropyl]dimethylamine
693221-12-4P, [(2R,3R)-3-(Benzofuran-7-yloxy)-2-fluoro-3-phenylpropyl]dimethylamine
693221-13-5P, [(2S,3S)-3-(2-Methylbenzofuran-7-yloxy)-2-fluoro-3-phenylpropyl]dimethylamine
693221-14-6P, [(2R,3S)-3-(Benzofuran-7-yloxy)-2-fluoro-3-phenylpropyl]dimethylamine
693221-15-7P, (1S,2R)-3-Methylamino-1-(naphthalen-1-yloxy)-1-phenylpropan-2-ol hydrochloride
693221-16-8P, (1R,2S)-3-Methylamino-1-(naphthalen-1-yloxy)-1-phenylpropan-2-ol hydrochloride
693221-17-9P, (1S,2R)-1-(Benzofuran-7-yloxy)-3-methylamino-1-phenylpropan-2-ol hydrochloride
693221-18-0P, (1S,2R)-1-(7-Fluorobenzothiophen-4-yloxy)-3-methylamino-1-phenylpropan-2-ol hydrochloride
693221-19-1P, (1R,2S)-1-(7-Fluorobenzothiophen-4-yloxy)-3-methylamino-1-phenylpropan-2-ol hydrochloride
693221-20-4P, (1R,2S)-1-(Benzo[d]isothiazol-4-yloxy)-3-methylamino-1-phenylpropan-2-ol hydrochloride
693221-21-5P, (1R,2S)-1-(Benzothiophen-7-yloxy)-3-methylamino-1-phenylpropan-2-ol Hydrochloride
693221-22-6P, (1S,2R)-1-(Benzothiophen-4-yloxy)-3-methylamino-1-phenylpropan-2-ol hydrochloride
693221-23-7P, (1R,2S)-1-((Benzothiophen-4-yl)oxy)-3-methylamino-1-phenylpropan-2-ol hydrochloride
693221-24-8P, (1S,2R)-1-(4-Fluoronaphthalen-1-yloxy)-1-(3-fluorophenyl)-3-methylaminopropan-2-ol hydrochloride
693221-25-9P, (1S,2R)-1-(Benzothiophen-4-yloxy)-1-(3-fluorophenyl)-3-methylaminopropan-2-ol Hydrochloride
693221-26-0P, (1R,2S)-1-(Benzothiophen-4-yloxy)-1-(3-fluorophenyl)-3-methylaminopropan-2-ol Hydrochloride
693221-27-1P, (1S,2R)-1-(5-Fluorobenzothiophen-4-yloxy)-1-(3-fluorophenyl)-3-methylaminopropan-2-ol hydrochloride
693221-28-2P, (1S,2R)-1-(Benzothiophen-7-yloxy)-3-methylamino-1-phenylpropan-2-ol hydrochloride
693221-29-3P, (1R,2S)-1-(Benzothiophen-4-ylsulfanyl)-3-methylamino-1-phenylpropan-2-ol
693221-30-6P, (1S,2R)-1-(Benzothiophen-4-ylsulfanyl)-3-methylamino-1-phenylpropan-2-ol
693221-31-7P, (1S,2R)-1-(Benzothiophen-7-ylsulfanyl)-3-methylamino-1-phenylpropan-2-ol
693221-32-8P, (1S,2R)-1-(2-Chlorophenylsulfanyl)-3-methylamino-1-phenylpropan-2-ol
693221-33-9P, (1R,2S)-1-(2-Chlorophenylsulfanyl)-3-methylamino-1-phenylpropan-2-ol
693221-34-0P, (1S,2R)-1-(2-Fluorobenzothiophen-4-yloxy)-3-methylamino-1-phenylpropan-2-ol
693221-35-1P, (1R,2S)-1-(2-Fluorobenzothiophen-4-yloxy)-3-methylamino-1-phenylpropan-2-ol
693221-36-2P, (1R,2R)-1-(Benzothiophen-7-yloxy)-3-methylamino-1-phenylpropan-2-ol Hydrochloride
693221-37-3P, (1S,2S)-1-(Benzothiophen-7-yloxy)-3-methylamino-1-phenylpropan-2-ol Hydrochloride
693221-38-4P, (1S,2S)-1-(Benzothiophen-4-yloxy)-3-methylamino-1-phenylpropan-2-ol Hydrochloride
693221-39-5P, (1R,2R)-1-(Benzothiophen-4-yloxy)-3-

methylamino-1-phenylpropan-2-ol Hydrochloride 693221-40-8P,
 (1R,2R)-3-Amino-1-(benzothiophen-7-yloxy)-1-phenylpropan-2-ol
 hydrochloride 693221-41-9P, (1R,2R)-1-(Benzothiophen-7-yloxy)-3-
 ethylamino-1-phenylpropan-2-ol hydrochloride 693221-42-0P,
 (1S,2R)-3-Amino-1-(naphthalen-1-yloxy)-1-phenylpropan-2-ol hydrochloride
 693221-43-1P, (1S,2R)-3-Dimethylamino-1-(naphthalen-1-yloxy)-1-
 phenylpropan-2-ol hydrochloride 693221-45-3P, [(2R,3S)-2-Methoxy-3-
 (naphthalen-1-yloxy)-3-phenylpropyl]methylamine hydrochloride
 693221-48-6P, [(2R,3S)-2-Benzyloxy-3-(naphthalen-1-yloxy)-3-
 phenylpropyl]methylamine hydrochloride 693221-49-7P,
 (1R,2R)-1-(7-Fluorobenzothiophen-4-yloxy)-3-methylamino-1-phenylpropan-2-
 ol hydrochloride 693221-50-0P, [(2S,3S)-2-Fluoro-3-(naphthalen-1-yloxy)-
 3-phenylpropyl]methylamine hydrochloride 693221-51-1P,
 [(2R,3R)-2-Fluoro-3-(naphthalen-1-yloxy)-3-phenylpropyl]methylamine
 hydrochloride 693221-52-2P, [(2S,3S)-3-(Benzofuran-7-yloxy)-2-fluoro-3-
 phenylpropyl]methylamine hydrochloride 693221-53-3P,
 [(2S,3R)-3-(Benzothiophen-4-yloxy)-2-fluoro-3-phenylpropyl]methylamine
 hydrochloride 693221-54-4P, [(2S,3S)-3-(Benzothiophen-4-yloxy)-2-fluoro-
 3-phenylpropyl]methylamine hydrochloride 693221-55-5P,
 [(2R,3R)-3-(Benzothiophen-4-yloxy)-2-fluoro-3-phenylpropyl]methylamine
 hydrochloride 693221-56-6P, [(2R,3S)-3-(Benzothiophen-4-yloxy)-2-fluoro-
 3-phenylpropyl]methylamine hydrochloride 693221-57-7P,
 [(2R,3R)-3-(Benzofuran-7-yloxy)-2-fluoro-3-phenylpropyl]methylamine
 hydrochloride 693221-58-8P, [(2S,3S)-3-(2-Methylbenzofuran-7-yloxy)-2-
 fluoro-3-phenylpropyl]methylamine hydrochloride 693221-59-9P,
 [(2R,3S)-3-(Benzofuran-7-yloxy)-2-fluoro-3-phenylpropyl]methylamine
 hydrochloride 693221-62-4P, [(2S,3S)-2-Fluoro-3-(5-fluorobenzothiophen-4-
 yloxy)-3-(3-fluorophenyl)propyl]dimethylamine 693221-63-5P,
 [(2S,3S)-3-(Benzothiophen-4-yloxy)-2-fluoro-3-(3-
 fluorophenyl)propyl]methylamine hydrochloride 693221-64-6P,
 [(2S,3S)-2-Fluoro-3-(5-fluorobenzothiophen-4-yloxy)-3-(3-
 fluorophenyl)propyl]methylamine hydrochloride
 RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU
 (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES
 (Uses)

(preparation of 3-aryloxy/thio-2,3-substituted propanamines and their use in
 inhibiting serotonin and norepinephrine
 reuptake)

IT 78-95-5, Chloroacetone 79-44-7, N,N-Dimethylcarbonyl chloride
 90-15-3, 1-Naphthol 100-39-0, Benzyl bromide 107-14-2,
 Chloroacetonitrile 107-21-1, 1,2-Ethanediol, reactions 108-98-5,
 Benzenethiol, reactions 141-82-2, Malonic acid, reactions 394-50-3,
 3-Fluoro-2-hydroxybenzaldehyde 452-08-4, 2-Bromo-4-fluoroanisole
 459-60-9, 4-Fluoroanisole 591-35-5, 3,5-Dichlorophenol 673-22-3,
 2-Hydroxy-4-methoxybenzaldehyde 758-16-7, N,N-Dimethylthioformamide
 928-95-0, trans-2-Hexen-1-ol 2032-35-1, Bromoacetaldehyde diethyl acetal
 2365-48-2, Methyl thioglycolate 2439-68-1, 5-Benzyloxy-1-methyl-1H-
 indole 5464-79-9, 2-Amino-4-methoxybenzothiazole 6320-03-2,
 2-Chlorothiophenol 7168-85-6, 7-Methoxy-1-benzofuran 7217-59-6,
 2-Methoxybenzenethiol 7507-86-0, 2-Bromo-5-methoxybenzaldehyde
 13414-95-4, 6,7-Dihydrobenzothiophen-4(5H)-one 16420-13-6,
 N,N-Dimethylthiocarbonyl chloride 19158-51-1, Tosyl cyanide
 19415-51-1, 5-Fluoro-2-methoxybenzaldehyde 20289-27-4,
 7-Benzyloxy-1H-indole 20595-30-6 50893-53-3, 1-Chloroethyl
 chloroformate 88791-12-2, 4-Bromo-7-methoxybenzothiophene 91420-78-9
 98819-68-2, (2R,3R)-3-Phenylglycidol 104196-23-8, (2S,3S)-3-
 Phenylglycidol 105728-90-3, 2-Fluoro-5-methoxybenzaldehyde 107643-29-8
 115144-40-6, 3,4-Difluoroanisole 137654-20-7, 2-Fluoro-3-methoxybenzoic
 acid 146137-74-8, 2-Fluoro-6-methoxybenzaldehyde 147460-41-1,

2-Bromo-5-fluorophenol 324769-10-0, 7-Bromo-6-fluorobenzothiophene
476198-97-7, 5-Fluoro-4-methoxybenzothiophene-2-carboxylic acid
476199-14-1, 4-Methoxybenzothiophene-2-carboxylic acid 693221-44-2,
(1S,2R)-3-Amino-1-(naphthalen-1-yloxy)-1-phenylpropan-2-ol 693221-47-5,
(1S,2R)-3-Methylamino-1-(naphthalen-1-yloxy)-1-phenylpropan-2-ol

RL: RCT (Reactant); RACT (Reactant or reagent)

(preparation of 3-aryloxy/thio-2,3-substituted propanamines and their use in
inhibiting serotonin and norepinephrine
reuptake)

IT 450-88-4P, 2-Bromo-5-fluoroanisole 2513-49-7P, 5-Bromo-6,7-
dihydrobenzothiophen-4(5H)-one 3048-46-2P, 4-Methoxybenzothiazole
3610-02-4P, 1-Benzothiophen-4-ol 4790-81-2P, 1-Benzofuran-7-ol
7405-23-4P, 4-Hydroxybenzothiazole 7651-82-3P, Isoquinolin-6-ol
13523-92-7P, 1-Methyl-1H-indol-5-ol 35272-30-1P, 4-
Methoxybenzo[d]isothiazole 52986-70-6P, 6-Methoxyisoquinoline
56724-09-5P, 5-Methoxy-2-methylbenzaldehyde 59845-54-4P,
4-Methylbenzothiophen-7-ol 67982-15-4P, Benzo[d]isothiazol-4-ol
74266-68-5P, 3-Fluoro-2-methoxybenzaldehyde 77898-35-2P,
Benzothiophen-7-ol 88791-08-6P 88791-18-8P, 7-Methoxybenzothiophene-2-
carbonitrile 88791-26-8P, 7-Methoxybenzo[d]isothiazole 92014-05-6P,
6-Methoxybenzothiophene-2-carbonitrile 92418-71-8P 94019-87-1P,
4-Cyano-7-hydroxybenzothiophene 96803-64-4P, 1-[(2,2-Diethoxyethyl)thio]-
2-methoxybenzene 98015-07-7P, 4-Bromo-3-(1,3-dioxolan-2-yl)phenyl methyl
ether 103438-88-6P, 2-Fluoro-3-methoxybenzaldehyde 125872-67-5P,
(E)-3-(3-Fluorophenyl)prop-2-en-1-ol 147317-39-3P, Benzo[d]isothiazol-7-
ol 170282-84-5P, 3-(1,3-Dioxolan-2-yl)-4-methylphenyl methyl ether
176095-56-0P, 2-Methylbenzofuran-7-ol 187543-87-9P, 2,3-Difluoro-6-
methoxybenzaldehyde 217099-77-9P, 6-Hydroxybenzothiophene-2-carbonitrile
398456-80-9P, 4-Fluoro-2-methoxybenzenethiol 446873-57-0P,
5-(2-Fluoro-5-methoxybenzylidene)-2-thioxo-1,3-thiazolidin-4-one
475577-33-4P, 1-Methyl-1H-indol-7-ol 475577-34-5P, 7-Benzyloxy-1-methyl-
1H-indole 476198-74-0P, 3-Methoxy-5-trifluoromethylbenzenethiol
476198-75-1P, 1-[(5-Fluoro-2-methoxyphenyl)sulfanyl]acetone
476198-76-2P, 1-[(2-Fluoro-5-methoxyphenyl)sulfanyl]acetone
476198-77-3P, 1-[(2,2-Diethoxyethyl)thio]-4-fluoro-2-methoxybenzene
476198-78-4P, 1-[(2,2-Diethoxyethyl)thio]-3-methoxy-5-
trifluoromethylbenzene 476198-79-5P, 5-Fluorobenzothiophen-7-yl methyl
ether 476198-80-8P, 4-Trifluoromethylbenzothiophen-6-yl methyl ether
476198-81-9P, 4-Fluoro-7-methoxybenzothiophene 476198-84-2P,
5-(3-Fluoro-2-methoxybenzylidene)-2-thioxo-1,3-thiazolidin-4-one
476198-86-4P, 5-(2-Methyl-5-methoxybenzylidene)-2-thioxo-1,3-thiazolidin-4-
one 476198-88-6P, (Z)-3-(2-Fluoro-5-methoxyphenyl)-2-mercapto-2-
propenoic acid 476198-90-0P, (Z)-3-(3-Fluoro-2-methoxyphenyl)-2-mercapto-
2-propenoic acid 476198-91-1P, (Z)-3-(2-Methyl-5-methoxyphenyl)-2-
mercapto-2-propenoic acid 476198-92-2P, 4-Fluoro-7-methoxybenzothiophene-
2-carboxylic acid 476198-93-3P, 4-Methyl-7-methoxybenzothiophene-2-
carboxylic acid 476198-95-5P, 4-Methyl-7-methoxybenzothiophene
476198-96-6P, 5-Fluoro-4-methoxybenzothiophene 476198-98-8P,
7-Fluoro-4-methoxybenzothiophene 476198-99-9P, 2-(5-Fluoro-2-
methoxyphenyl)-2-hydroxy-N,N-dimethylethanethioamide 476199-00-5P,
(7-Fluoro-4-methoxybenzothiophen-2-yl)dimethylamine 476199-01-6P,
7-Fluoro-4-methoxybenzothiophen-2(3H)-one 476199-02-7P, Methyl
7-fluoro-4-methoxybenzothiophene-2-carboxylate 476199-03-8P,
7-Fluoro-4-methoxybenzothiophene-2-carboxylic acid 476199-04-9P,
3-Chloro-4-fluoro-7-methoxybenzothiophene 476199-05-0P,
(E)-3-(2-Fluoro-5-methoxyphenyl)-2-propenoic acid 476199-06-1P, Methyl
3-chloro-4-fluoro-7-methoxybenzothiophene-2-carboxylate 476199-07-2P,
3-Chloro-4-fluoro-7-methoxybenzothiophene-2-carboxylic acid
476199-08-3P, 4-Fluoro-7-methoxy-3-methylbenzothiophene 476199-09-4P,

7-Fluoro-4-methoxy-3-methylbenzothiophene 476199-10-7P,
2-Fluoro-7-methoxybenzothiophene 476199-11-8P, 2-Fluoro-4-methoxybenzothiophene 476199-12-9P, 2-Iodo-7-methoxybenzothiophene 476199-13-0P, 4-Methoxybenzothiophene-2-carbonitrile 476199-15-2P, 4-Fluoro-7-methoxybenzothiophene-2-carbonitrile 476199-16-3P, 4-Fluoro-7-methoxybenzothiophene-2-carboxamide 476199-17-4P, 4-Cyano-7-methoxybenzothiophene 476199-18-5P, O-(2-Formyl-5-methoxyphenyl)dimethylthiocarbamate 476199-19-6P, S-(2-Formyl-5-methoxyphenyl)dimethylthiocarbamate 476199-20-9P, 5-Fluorobenzothiophen-7-ol 476199-21-0P, 4-Trifluoromethylbenzothiophen-6-ol 476199-22-1P, 5-Fluorobenzothiophen-4-ol 476199-23-2P, 7-Fluorobenzothiophen-4-ol 476199-24-3P, 3-Chloro-4-fluorobenzothiophen-7-ol 476199-25-4P, 3-Methyl-4-fluorobenzothiophen-7-ol 476199-26-5P, 7-Fluoro-3-methylbenzothiophen-4-ol 476199-27-6P, 2-Fluorobenzothiophen-7-ol 476199-28-7P, 2-Fluorobenzothiophen-4-ol 476199-29-8P, 7-Hydroxybenzothiophene-2-carbonitrile 476199-30-1P, 4-Hydroxybenzothiophene-2-carbonitrile 476199-31-2P, 4-Fluoro-7-hydroxybenzothiophene-2-carbonitrile 476199-32-3P, 6-Fluorobenzothiophen-7-ol 507477-13-6P, 5-Fluoro-6,7-dihydro-5H-benzothiophen-4-one 693220-39-2P, 5-Bromo-5-fluoro-6,7-dihydro-5H-benzothiophen-4-one 693220-40-5P 693220-41-6P 693220-42-7P 693220-43-8P 693220-44-9P, 7-Methylbenzo[d]isothiazol-4-ol 693220-45-0P, 7-Bromo-4-methoxybenzo[d]isothiazole 693220-46-1P, 4-Methoxy-7-methylbenzo[d]isothiazole 693220-47-2P 693220-48-3P, 4-Fluoro-2,3-dihydrobenzothiophen-7-ol 693220-49-4P, 4-Fluoro-7-methoxy-2,3-dihydrobenzothiophene 693220-50-7P, [(2R,3R)-3-(3-Fluorophenyl)oxiranyl]methanol 693220-51-8P, [(2S,3S)-3-(3-Fluorophenyl)oxiranyl]methanol 693220-52-9P, (2R,3S)-3-(Naphthalen-1-yloxy)-3-phenylpropane-1,2-diol 693220-53-0P, (2R,3S)-3-(Benzothiophen-4-yloxy)-3-phenylpropane-1,2-diol 693220-54-1P, (2R,3S)-3-(7-Fluorobenzothiophen-4-yloxy)-3-phenylpropane-1,2-diol 693220-55-2P, (2R,3S)-3-(2-Methylbenzofuran-7-yloxy)-3-phenylpropane-1,2-diol 693220-56-3P, (2R,3S)-3-(Benzofuran-7-yloxy)-3-phenylpropane-1,2-diol 693220-57-4P, (2R,3S)-3-[[Benzo[d]isothiazol-4-yl]oxy]-3-phenylpropane-1,2-diol 693220-58-5P, (2R,3S)-3-(Benzothiophen-7-yloxy)-3-phenylpropane-1,2-diol 693220-59-6P, (2R,3S)-3-(2-Fluorobenzothiophen-4-yloxy)-3-phenylpropane-1,2-diol 693220-60-9P, (2S,3R)-3-(Naphthalen-1-yloxy)-3-phenylpropane-1,2-diol 693220-61-0P 693220-62-1P, (2S,3R)-3-[(Benzo[d]isothiazol-4-yl)oxy]-3-phenylpropane-1,2-diol 693220-63-2P, (2S,3R)-3-(Benzothiophen-7-yloxy)-3-phenylpropane-1,2-diol 693220-64-3P, (2R,3S)-3-(Benzothiophen-4-yloxy)-3-(3-fluorophenyl)propane-1,2-diol 693220-65-4P, (2R,3S)-3-(4-Fluoronaphthalen-1-yloxy)-3-(3-fluorophenyl)propane-1,2-diol 693220-66-5P, (2R,3S)-3-(5-Fluorobenzothiophen-4-yloxy)-3-(3-fluorophenyl)propane-1,2-diol 693220-67-6P, (2S,3R)-3-(Benzothiophen-4-yloxy)-3-(3-fluorophenyl)propane-1,2-diol 693220-68-7P, (2S,3R)-3-(Benzothiophen-4-ylsulfanyl)-3-phenylpropane-1,2-diol 693220-69-8P, (2R,3S)-3-(Benzothiophen-4-ylsulfanyl)-3-phenylpropane-1,2-diol 693220-70-1P, (2R,3S)-3-(2-Chlorophenylsulfanyl)-3-phenylpropane-1,2-diol 693220-71-2P, (2S,3R)-3-(2-Chlorophenylsulfanyl)-3-phenylpropane-1,2-diol 693220-72-3P 693220-73-4P 693220-74-5P 693220-75-6P 693220-76-7P, (1R,2R)-3-Azido-1-(benzothiophen-4-yloxy)-1-phenylpropan-2-ol 693220-77-8P, (1S,2S)-3-Azido-1-(benzothiophen-4-yloxy)-1-phenylpropan-2-ol 693220-78-9P, (1S,2R)-3-Azido-1-(naphthalen-1-yloxy)-1-phenylpropan-2-ol 693220-79-0P, (1R,2S)-3-Azido-1-(naphthalen-1-yloxy)-1-phenylpropan-2-ol 693220-80-3P, (2R,3S)-1-Azido-3-((benzofuran-7-yl)oxy)-3-phenylpropan-2-ol 693220-81-4P, (1R,2S)-3-Azido-1-(benzofuran-7-yloxy)-1-phenylpropan-2-ol 693220-82-5P, (1S,2R)-3-Azido-1-(2-methylbenzofuran-7-yloxy)-1-phenylpropan-2-ol 693220-83-6P, (1S,2R)-3-Azido-1-(benzothiophen-4-

yloxy)-1-phenylpropan-2-ol 693220-84-7P, (1R,2S)-3-Azido-1-(benzothiophen-4-yloxy)-1-phenylpropan-2-ol 693220-85-8P, Toluene-4-sulfonic acid (2R,3S)-3-(benzothiophen-4-yloxy)-2-hydroxy-3-phenylpropyl ester 693220-86-9P, Toluene-4-sulfonic acid (2R,3S)-3-(5-fluorobenzothiophen-4-yloxy)-3-(3-fluorophenyl)-2-hydroxypropyl ester 693220-87-0P, (1R,2S)-3-Azido-1-(5-fluorobenzothiophen-4-yloxy)-1-(3-fluorophenyl)propan-2-ol 693220-88-1P, 4-(((1S,2S)-3-Azido-2-fluoro-1-phenylpropyl)oxy)benzothiophene 693220-89-2P, 4-(((1S,2S)-3-Azido-2-fluoro-1-(3-fluorophenyl)propyl)oxy)-5-fluorobenzothiophene 693220-90-5P, (2R,3S)-3-(3,5-Dichlorophenoxy)hexane-1,2-diol 693220-91-6P, (2R,3S)-3-(2,4-Dichlorophenoxy)hexane-1,2-diol 693220-92-7P, Toluene-4-sulfonic acid (2S,3S)-3-(3,5-dichlorophenoxy)-2-hydroxyhexyl ester 693220-93-8P, Toluene-4-sulfonic acid (2S,3S)-3-(2,4-dichlorophenoxy)-2-hydroxyhexyl ester 693221-46-4P, 2,2-Difluoro-N-[(2R,3S)-2-hydroxy-3-(naphthalen-1-yloxy)-3-phenylpropyl]-N-methylacetamide

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(preparation of 3-aryloxy/thio-2,3-substituted propanamines and their use in inhibiting serotonin and norepinephrine reuptake)

REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 161 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2004:267228 HCAPLUS

DOCUMENT NUMBER: 140:264524

TITLE: Method using an estrogen receptor β selective agonist alone or in combination with other agents for treating depression, anxiety, and dementia

INVENTOR(S): Rohrer, Susan P.; Hammond, Milton L.

PATENT ASSIGNEE(S): Merck & Co., Inc., USA

SOURCE: PCT Int. Appl., 41 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004026290	A1	20040401	WO 2003-US29068	20030915
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW			
RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG			
EP 1542665	A1	20050622	EP 2003-749711	20030915
R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK			
PRIORITY APPLN. INFO.:			US 2002-411919P	P 20020919
			WO 2003-US29068	W 20030915

AB This invention relates to the treatment and/or prevention of depression and/or anxiety disorders and/or dementia by the administration of an

estrogen receptor β selective agonist either as a single agent, or in combination with other agents.

IC ICM A61K031-12

ICS A61K031-34; A61K031-41; A61K031-415

CC 1-11 (Pharmacology)

IT **Mental disorder**

(anger management; estrogen receptor β selective agonist alone or with other agents for treating **depression**, anxiety, and dementia)

IT **Mental disorder**

(attention deficit disorder; estrogen receptor β selective agonist alone or with other agents for treating **depression**, anxiety, and dementia)

IT **Mental disorder**

(bipolar disorder; estrogen receptor β selective agonist alone or with other agents for treating **depression**, anxiety, and dementia)

IT **Mental disorder**

(cognitive, mild cognitive impairment; estrogen receptor β selective agonist alone or with other agents for treating **depression**, anxiety, and dementia)

IT **Mental disorder**

(dementia; estrogen receptor β selective agonist alone or with other agents for treating **depression**, anxiety, and dementia)

IT **Mental disorder**

(**depression**; estrogen receptor β selective agonist alone or with other agents for treating **depression**, anxiety, and dementia)

IT **Mental disorder**

(impulsivity; estrogen receptor β selective agonist alone or with other agents for treating **depression**, anxiety, and dementia)

IT **Mental disorder**

(irritability; estrogen receptor β selective agonist alone or with other agents for treating **depression**, anxiety, and dementia)

IT **Mental disorder**

(obsession-compulsion; estrogen receptor β selective agonist alone or with other agents for treating **depression**, anxiety, and dementia)

IT **Mental disorder**

(postpartum **depression**; estrogen receptor β selective agonist alone or with other agents for treating **depression**, anxiety, and dementia)

IT 50-47-5, Desipramine 50-48-6, Amitriptyline 50-49-7, Imipramine 51-71-8, Phenelzine 59-63-2, Isocarboxazid 72-69-5, Nortriptyline

155-09-9, Tranylcypromine 303-49-1, Clomipramine 438-60-8,

Protriptyline 739-71-9, Trimipramine 1406-16-2, Vitamin D

1406-16-2D, Vitamin D, analogs 1668-19-5, Doxepin 7439-93-2, Lithium,

biological studies 9002-64-6, Parathyroid hormone 9007-12-9,

Calcitonin 10262-69-8, Maprotiline 14028-44-5, Amoxapine 14611-51-9,

Selegiline 19794-93-5, Trazodone 34911-55-2, Bupropion 46817-91-8,

Viloxazine 54739-18-3, Fluvoxamine 54910-89-3, Fluoxetine

61869-08-7, Paroxetine 71320-77-9, Moclobemide 79617-96-2, Sertraline

83366-66-9, Nefazodone 93413-69-5, Venlafaxine

RL: PAC (Pharmacological activity); THU (Therapeutic

use); BIOL (Biological study); USES (Uses)

(estrogen receptor β selective agonist alone or with other agents for treating **depression**, anxiety, and dementia)

REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 162 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN
 ACCESSION NUMBER: 2004:100942 HCAPLUS
 DOCUMENT NUMBER: 140:139528
 TITLE: Combination therapy for depression, prevention of
 suicide, and various medical and psychiatric
 conditions
 INVENTOR(S): Migaly, Peter
 PATENT ASSIGNEE(S): USA
 SOURCE: PCT Int. Appl., 28 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004010932	A2	20040205	WO 2003-US23326	20030725
WO 2004010932	A3	20040722		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2004204401	A1	20041014	US 2003-627358	20030725
EP 1551393	A2	20050713	EP 2003-748977	20030725
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
PRIORITY APPLN. INFO.:			US 2002-319436P	P 20020730
			WO 2003-US23326	W 20030725

AB The present invention relates to a new method of treatment for persons meeting diagnoses for major depressive disorder, or other unipolar (non-bipolar, nonpsychotic and non-treatment resistant) depression. The method comprises administering a combination of two categories of drugs, antipsychotics or dopamine system stabilizers, in combination with a newer antidepressant such as a selective serotonin reuptake inhibitor, as initial treatment or as soon as possible. The method targets the prevention of suicide, and provides other benefits including preventing disease progression development of tolerance toward the antidepressants. Another aspect of the invention relates to using the method for alleviating cognitive distortion and related functional impairment or health risks, and/or using the method for smoking cessation or nicotine withdrawal.

IC ICM A61K

CC 1-11 (Pharmacology)

Section cross-reference(s): 2, 4

IT **Mental disorder**

(cognitive; combination therapy for **depression**, prevention of suicide, and various medical and psychiatric conditions)

IT **Mental disorder**

(**depression**, delusional; combination therapy for **depression**, prevention of suicide, and various medical and psychiatric conditions)

IT **Mental disorder**
 (depression; combination therapy for depression,
 prevention of suicide, and various medical and psychiatric conditions)

IT **Mental disorder**
 (major depression; combination therapy for depression
 , prevention of suicide, and various medical and psychiatric
 conditions)

IT **Mental disorder**
 (unipolar depression; combination therapy for
 depression, prevention of suicide, and various medical and
 psychiatric conditions)

IT 53-43-0, Dehydroepiandrosterone 58-05-9, Folinic acid 58-39-9,
 Perphenazine 73-22-3, Tryptophan, biological studies 117-89-5,
 Trifluoperazine 303-49-1, Clomipramine 2709-56-0, Flupenthixol
 3575-80-2, Melperone 15676-16-1, Sulpiride 26615-21-4, Zotepine
 27203-92-5, Tramadol 34911-55-2, Bupropion 35604-67-2, Viloxazine
 hydrochloride 54739-18-3, Fluvoxamine 54910-89-3, Fluoxetine
 56775-88-3, Zimelidine 59729-33-8, Citalopram 59859-58-4, Femoxetine
 60719-82-6, Alaproclate 61869-08-7, Paroxetine 63758-79-2, Indalpine
 71620-89-8, Reboxetine 71675-85-9, Amisulpride 75558-90-6, Amperozide
 79617-96-2, Sertraline 83366-66-9, Nefazodone 83891-03-6,
 Norfluoxetine 83928-76-1, Gepirone 85650-52-8, Mirtazapine
 85650-56-2, Org 5222 92623-85-3, Milnacipran 93413-69-5
 , Venlafaxine 106266-06-2, Risperidone 111974-69-7, Quetiapine
 116539-59-4, Duloxetine 128196-01-0, Escitalopram 129273-38-7,
 SM-9018 129722-12-9, Aripiprazole 132539-06-1, Olanzapine
 133454-47-4, Iloperidone 146939-27-7, Ziprasidone 149859-10-9, JL-13
 RL: PAC (Pharmacological activity); THU (Therapeutic
 use); BIOL (Biological study); USES (Uses)
 (combination therapy for depression, prevention of suicide,
 and various medical and psychiatric conditions)

L91 ANSWER 163 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN
 ACCESSION NUMBER: 2004:1036769 HCAPLUS
 DOCUMENT NUMBER: 141:420471
 TITLE: Treatment of refractory depression with an opiate
 antagonist and an antidepressant
 INVENTOR(S): Glover, Hillel
 PATENT ASSIGNEE(S): USA
 SOURCE: U.S. Pat. Appl. Publ., 11 pp., Cont.-in-part of U.S.
 Ser. No. 925,190, abandoned.
 CODEN: USXXCO
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 2
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004242974	A1	20041202	US 2004-878285	20040629
US 2003087896	A1	20030508	US 2001-925190	20010809
PRIORITY APPLN. INFO.:			US 2001-925190	B2 20010809
AB An antidepressant or a pharmaceutically acceptable salt thereof, and an opiate antagonist or a pharmaceutically acceptable salt thereof, are used to treat refractory depression characterized by dissociation				
IC ICM A61B005-00 ICS G06F019-00; G01N033-48; G01N033-50				
INCL 600300000; 702019000				
CC 1-11 (Pharmacology)				

IT **Mental disorder**
 (depression; opiate antagonist and antidepressant for treatment of refractory **depression** with dissociation)

IT **Mental disorder**
 (dissociation; opiate antagonist and antidepressant for treatment of refractory **depression** with dissociation)

IT 50-48-6, Amitriptyline 50-49-7, Imipramine 72-69-5, Nortriptyline
 23047-25-8, Lofepramine 29908-03-0, SAM-E 34911-55-2, Bupropion SR
 54739-18-3, Fluvoxamine 54910-89-3, Fluoxetine 59729-33-8, Citalopram
 61869-08-7, Paroxetine 71620-89-8, Reboxetine 79617-96-2, Sertraline
 83366-66-9, Nefazodone 85650-52-8, Mirtazapine 93413-69-5,
 Venlafaxine

RL: **PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)**
 (opiate antagonist and antidepressant for treatment of refractory **depression** with dissociation)

L91 ANSWER 164 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN
 ACCESSION NUMBER: 2004:142815 HCAPLUS
 DOCUMENT NUMBER: 140:157480
 TITLE: Monoamine reuptake inhibitors for the treatment and prevention of **depression secondary to pain**

INVENTOR(S): Rao, Srinivas G.; Kranzler, Jay D.
 PATENT ASSIGNEE(S): Cypress Bioscience, Inc., USA
 SOURCE: U.S. Pat. Appl. Publ., 13 pp., Cont.-in-part of U.S. Ser. No. 28,547.
 CODEN: USXXCO

DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 5
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004034101	A1	20040219	US 2003-628141	20030724
US 2003139476	A1	20030724	US 2001-14149	20011105
US 6635675	B2	20031021		
US 2003130353	A1	20030710	US 2001-28547	20011219
US 6602911	B2	20030805		
PRIORITY APPLN. INFO.:			US 2001-14149	A2 20011105
			US 2001-28547	A2 20011219
			US 2002-398676P	P 20020724
			US 2003-443035P	P 20030128

AB Methods for the prevention or treatment of a typical **depression secondary to pain (DSP)** have been developed. The method generally involves administering an effective amount of a monoamine reuptake inhibitor to treat or prevent symptoms of **DSP**. In a preferred embodiment, a therapeutically effective amount of a dual **serotonin/norepinephrine reuptake inhibitor (SNRI)** compound of a specific type, or a pharmaceutically acceptable salt thereof, is administered. The most preferred SNRI compds. are non-tricyclic SNRIs, wherein serotonin reuptake inhibition is greater than norepinephrine reuptake inhibition; and **NSRIs**, wherein norepinephrine reuptake inhibition is greater than serotonin reuptake inhibition. The most preferred compound is milnacipran, or a bioequivalent or pharmaceutically acceptable salt thereof. Other preferred compds. are duloxetine and venlafaxine or a bioequivalent or pharmaceutically acceptable salt thereof. In yet another embodiment, a therapeutically

effective amount of a non-tricyclic **triple reuptake inhibitor** (TRI) compound of a specific type, or a pharmaceutically acceptable salt thereof, is administered. The TRI compds. are characterized by their ability to block the reuptake (and hence increase central concns. of) the three primary brain monoamines: serotonin, noradrenaline, and dopamine.

- IC ICM A61K031-165
- INCL 514619000
- CC 1-11 (Pharmacology)
- ST monoamine reuptake inhibitor **depression secondary to pain**; milnacipran duloxetine venlafaxine **depression secondary to pain**
- IT Glutamate antagonists
(NMDA antagonists; monoamine reuptake inhibitors for treatment and prevention of **depression secondary to pain**)
- IT **Pain**
(abdominal; monoamine reuptake inhibitors for treatment and prevention of **depression secondary to pain**)
- IT Disease, animal
(back **pain**, lower back; monoamine reuptake inhibitors for treatment and prevention of **depression secondary to pain**)
- IT Body, anatomical
(back, disease, **pain**, lower back; monoamine reuptake inhibitors for treatment and prevention of **depression secondary to pain**)
- IT **Pain**
(back, lower back; monoamine reuptake inhibitors for treatment and prevention of **depression secondary to pain**)
- IT Disease, animal
(chronic **pain** from; monoamine reuptake inhibitors for treatment and prevention of **depression secondary to pain**)
- IT **Pain**
(chronic; monoamine reuptake inhibitors for treatment and prevention of **depression secondary to pain**)
- IT **Mental disorder**
(**depression**; monoamine reuptake inhibitors for treatment and prevention of **depression secondary to pain**)
- IT Head
(face, myofascial face **pain**; monoamine reuptake inhibitors for treatment and prevention of **depression secondary to pain**)
- IT 5-HT reuptake inhibitors
Analgesics
Antidepressants
Drug delivery systems
Headache
Human
Pain
(monoamine reuptake inhibitors for treatment and prevention of **depression secondary to pain**)
- IT Emotion
(mood reactivity; monoamine reuptake inhibitors for treatment and prevention of **depression secondary to pain**)

- IT Nerve, disease
(neuropathy, neuropathic **pain**; monoamine reuptake inhibitors for treatment and prevention of **depression secondary to pain**)
- IT Nervous system
(neurovegetative symptoms; monoamine reuptake inhibitors for treatment and prevention of **depression secondary to pain**)
- IT Abdomen, disease
Neck, anatomical
(**pain**; monoamine reuptake inhibitors for treatment and prevention of **depression secondary to pain**)
- IT Body, anatomical
(pelvis, pelvic **pain**; monoamine reuptake inhibitors for treatment and prevention of **depression secondary to pain**)
- IT Biological transport
(reuptake; monoamine reuptake inhibitors for treatment and prevention of **depression secondary to pain**)
- IT Seizures
(risk; monoamine reuptake inhibitors for treatment and prevention of **depression secondary to pain**)
- IT Thorax
(typical chest **pain**; monoamine reuptake inhibitors for treatment and prevention of **depression secondary to pain**)
- IT 50-67-9, Serotonin, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(monoamine reuptake inhibitors for treatment and prevention of **depression secondary to pain**)
- IT 765-30-0D, Aminocyclopropane, derivs. 92623-85-3, Milnacipran
106650-56-0, Sibutramine
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(monoamine reuptake inhibitors for treatment and prevention of **depression secondary to pain**)
- IT 51-41-2, Norepinephrine 51-61-6, Dopamine, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(reuptake inhibitors; monoamine reuptake inhibitors for treatment and prevention of **depression secondary to pain**)

L91 ANSWER 165 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:1142843 HCAPLUS
DOCUMENT NUMBER: 143:18971
TITLE: Duloxetine: a dual reuptake inhibitor
AUTHOR(S): Dugan, Sara E.; Fuller, Matthew A.
CORPORATE SOURCE: Louis Stokes Cleveland Department of Veterans Affairs
Medical Center, Brecksville, OH, USA
SOURCE: Annals of Pharmacotherapy (2004), 38(12), 2078-2085
CODEN: APHRER; ISSN: 1060-0280
PUBLISHER: Harvey Whitney Books Co.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB OBJECTIVE: To review the pharmacol., pharmacokinetics, clin. efficacy, and safety profile of duloxetine for the treatment of major depressive disorder (MDD). DATA SOURCES: Searches using MEDLINE and PsycINFO were conducted (1966 to Nov. 2003). STUDY SELECTION AND DATA Extraction: All

duloxetine MDD information gathered was considered. Articles containing comprehensive information regarding duloxetine use for MDD were evaluated. DATA SYNTHESIS: Duloxetine is a serotonin-norepinephrine reuptake inhibitor being considered for treatment of MDD and stress urinary incontinence. While approved dosing ranges have not yet been determined, studies support the efficacy and safety of 40-60 mg twice daily for the treatment of acute MDD. Adverse effects have been of mild to moderate severity and are considered to be transient. Cardiovascular effects (increased heart rate or blood pressure), while present, do not appear to be clin. significant. Overall, duloxetine appears to be well tolerated. CONCLUSIONS: Duloxetine is a safe and effective antidepressant. Approval of this agent provides another treatment option for the management of MDD.

CC 1-0 (Pharmacology)

IT **Mental disorder**

(major **depression**; duloxetine is safe and effective antidepressant as shown by pharmacol. and pharmacokinetics and approval of this agent may provide treatment option for management of major depressive disorder in human)

IT **116539-59-4, Duloxetine**

RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(duloxetine is safe and effective antidepressant as shown by pharmacol. and pharmacokinetics and approval of this agent may provide treatment option for management of major **depressive** disorder in human)

REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 166 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2005:95111 HCAPLUS

DOCUMENT NUMBER: 143:38217

TITLE: Geriatric depression treatment in nonresponders to selective serotonin reuptake inhibitors

AUTHOR(S): Whyte, Ellen M.; Basinski, James; Farhi, Panthea; Dew, Mary Amanda; Begley, Amy; Mulsant, Benoit H.; Reynolds, Charles F., III

CORPORATE SOURCE: Department of Psychiatry, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA

SOURCE: Journal of Clinical Psychiatry (2004), 65(12), 1634-1641

CODEN: JCLPDE; ISSN: 0160-6689

PUBLISHER: Physicians Postgraduate Press, Inc.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Up to a third of elderly patients with major depressive disorder are treatment resistant, yet little objective evidence is available to guide the clinician in managing these patients. We report here our experience with elderly subjects with prospectively defined treatment-resistant depression in 2 sep. research studies: one entailing an augmentation strategy, the other a change to venlafaxine extended release (XR). Fifty-three elderly subjects with major depressive disorder according to DSM-IV criteria who failed treatment with paroxetine plus interpersonal psychotherapy received 1 to 3 trials of augmentation with bupropion sustained release, nortriptyline, or lithium. Successively fewer subjects entered each sequential trial of augmentation. Twelve subjects subsequently received venlafaxine XR monotherapy. Response to treatment was defined as a 17-item Hamilton Rating Scale for Depression score of < 10 for 3 wk. Sixty percent of subjects (N = 32) responded to some form of augmentation, with 45% (24/53), 31% (5/16), and 43% (3/7) responding to

the first, second, and third augmentation trials, resp. The mean time to response after starting the first augmentation trial was 6.0 (SD = 5.8) weeks. Forty-two percent (N = 5) of the venlafaxine XR-treated subjects responded with the mean time to response of 6.4 (SE = 0.9) weeks. Adverse effects leading to treatment discontinuation and falls were more common in the augmentation subjects than in the venlafaxine XR subjects. We observed similar rates and speed of response with an augmentation strategy and a strategy of switching to venlafaxine XR in elderly subjects with prospectively defined treatment-resistant major depressive disorder. Venlafaxine XR was generally better tolerated than the augmentation strategies. Further investigation of venlafaxine XR as a preferred strategy for treatment-resistant geriatric depression is warranted.

CC 1-11 (Pharmacology)

IT **Mental disorder**

(**depression**; selective serotonin reuptake inhibitor venlafaxine XR was well tolerated, effective with less adverse effects than augmentation strategies for treatment-resistant geriatric **depression** in human)

IT **Mental disorder**

(major **depression**; selective serotonin reuptake inhibitor venlafaxine XR was well tolerated, effective with less adverse effects than augmentation strategies for treatment-resistant major depressive disorder in human)

IT 93413-69-5, Venlafaxine

RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(selective serotonin reuptake inhibitor venlafaxine XR was well tolerated, effective with less adverse effects than augmentation strategies for treatment-resistant geriatric **depression** in human)

REFERENCE COUNT: 48 THERE ARE 48 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 167 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2004:446363 HCAPLUS

DOCUMENT NUMBER: 142:32787

TITLE: Dose-related Pathology after Topical Application to Rat Sciatic Nerve

AUTHOR(S): Estebe, Jean-Pierre; Myers, Robert R.

CORPORATE SOURCE: Service d'Anesthesie Reanimation 2, Centre Hospitalier Universitaire de Rennes, La Jolla, CA, USA

SOURCE: Anesthesiology (2004), 100(6), 1519-1525

CODEN: ANESAV; ISSN: 0003-3022

PUBLISHER: Lippincott Williams & Wilkins

DOCUMENT TYPE: Journal

LANGUAGE: English

AB BACKGROUND: Amitriptyline is a tricyclic **antidepressant** drug

used systemically for the management of neuropathic **pain**.

Antidepressants, as a class of drugs with direct neurol. actions, are becoming widely used for the management of chronic pain, although their mechanisms are not entirely understood. Amitriptyline exerts potent effects on reuptake of norepinephrine and

serotonin and **blocks** α_2 adrenoreceptors and

N-methyl-D-aspartate receptors. Because amitriptyline is also a particularly potent blocker of sodium channels and voltage-gated potassium and calcium channels, it has been recommended as a long-acting local anesthetic agent. Unfortunately, amitriptyline has significant toxic side effects in the central nervous system and cardiovascular system that are

dose-related to its systemic administration. Therefore, before amitriptyline can be used clin. as a local anesthetic agent, it should be thoroughly explored with respect to its direct neurotoxic effect in the peripheral nervous system. METHODS: The left sciatic nerve of Sprague-Dawley rats (12/ group) received a single topical amitriptyline dose of 0.625, 1.25, 2.5, or 5 mg; a saline group (n = 2) was used as control. Neuropathol. evaluations were conducted in sep. animals (n = 4) 1, 3, and 7 days later. RESULTS: Amitriptyline topically applied in vivo to rat sciatic nerve causes a dose-related neurotoxic effect. Drug doses of 0.625-5 mg all caused Wallerian degeneration of peripheral nerve fibers, with the number of affected fibers and the severity of the injury directly related to the dose. CONCLUSION: Because the effective local anesthetic dose is within this dose range, the authors strongly recommend that amitriptyline not be used as a local anesthetic agent.

CC 1-11 (Pharmacology)

Section cross-reference(s): 63

REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 168 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2004:339622 HCAPLUS

DOCUMENT NUMBER: 141:374627

TITLE: Selective serotonin reuptake inhibitors in childhood depression: systematic review of published versus unpublished data

AUTHOR(S): Whittington, Craig J.; Kendall, Tim; Fonagy, Peter; Cottrell, David; Cotgrove, Andrew; Boddington, Ellen

CORPORATE SOURCE: Centre for Outcomes Research and Effectiveness, Subdepartment of Clinical Health Psychology, University College London, London, WC1E 7HB, UK

SOURCE: Lancet (2004), 363(9418), 1341-1345

CODEN: LANCAO; ISSN: 0140-6736

PUBLISHER: Elsevier Science Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Background: Questions concerning the safety of selective serotonin reuptake inhibitors (SSRIs) in the treatment of depression in children led us to compare and contrast published and unpublished data on the risks and benefits of these drugs. Methods: We did a meta-anal. of data from randomized controlled trials that evaluated an SSRI vs. placebo in participants aged 5-18 yr and that were published in a peer-reviewed journal or were unpublished and included in a review by the Committee on Safety of Medicines. The following outcomes were included: remission, response to treatment, depressive symptom scores, serious adverse events, suicide-related behaviors, and discontinuation of treatment because of adverse events. Findings: Data for two published trials suggest that fluoxetine has a favorable risk-benefit profile, and unpublished data lend support to this finding. Published results from one trial of paroxetine and two trials of sertraline suggest equivocal or weak pos. risk-benefit profiles. However, in both cases, addition of unpublished data indicates that risks outweigh benefits. Data from unpublished trials of citalopram and venlafaxine show unfavorable risk-benefit profiles. Interpretation: Published data suggest a favorable risk-benefit profile for some SSRIs; however, addition of unpublished data indicates that risks could outweigh benefits of these drugs (except fluoxetine) to treat depression in children and young people. Clin. guideline development and clin. decisions about treatment are largely dependent on an evidence base published in peer-reviewed journals. Non-publication of trials, for whatever reason, or the omission of important data from published trials,

can lead to erroneous recommendations for treatment. Greater openness and transparency with respect to all intervention studies is needed.

CC 1-11 (Pharmacology)

IT **Mental disorder**

(**depression**; published data suggest favorable risk-benefit profile for some SSRIs while addition of unpublished data indicate risks could outweigh benefits of paroxetine, sertraline, citalopram, venlafaxine except fluoxetine to treat child **depression**)

IT 54910-89-3, Fluoxetine 59729-33-8, Citalopram 61869-08-7, Paroxetine 79617-96-2, Sertraline 93413-69-5, Venlafaxine

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(published data suggest favorable risk-benefit profile for some SSRIs while addition of unpublished data indicate risks could outweigh benefits of paroxetine, sertraline, citalopram, venlafaxine except fluoxetine to treat child **depression**)

REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 169 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2004:903324 HCAPLUS

DOCUMENT NUMBER: 142:190949

TITLE: Breastfeeding during maternal antidepressant treatment with serotonin reuptake inhibitors: infant exposure, clinical symptoms, and cytochrome P450 genotypes

AUTHOR(S): Berle, Jan Oystein; Steen, Vidar M.; Aamo, Trond Oskar; Breilid, Harald; Zahlsten, Kolbjorn; Spigset, Olav

CORPORATE SOURCE: Centre for Child and Adolescent Mental Health, University of Bergen, Bergen, Norway

SOURCE: Journal of Clinical Psychiatry (2004), 65(9), 1228-1234

CODEN: JCLPDE; ISSN: 0160-6689

PUBLISHER: Physicians Postgraduate Press, Inc.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The aims of the study were to quantify the drug exposure in breastfed infants of antidepressant-treated mothers, to identify possible adverse events, and to correlate these variables to maternal and infant drug metabolism-relevant genotypes and milk triglyceride content. The study included 25 lactating women treated with citalopram (N = 9), sertraline (N = 6), paroxetine (N = 6), fluoxetine (N = 1), or venlafaxine (N = 3) and their 26 breastfed infants. Drug concns. in maternal and infant serum and milk were analyzed using liquid chromatog. mass spectrometry methods; milk triglyceride levels were measured with a com. kit. Cytochrome P 450 (CYP) 2D6 and CYP2C19 activity was determined by polymerase chain reaction-based genotyping of the mothers and infants. An infant adverse event questionnaire was completed by the medication-treated mothers as well as by a control group of medication-free breastfeeding mothers of 68 infants. Sertraline and paroxetine were not detected in any of the drug-exposed infants. The infant serum level of citalopram was either undetectable (N = 4) or low (N = 6). All venlafaxine-exposed infants had measurable drug concns. We identified a paroxetine-treated mother and her infant who were both CYP2D6 poor metabolizers, as well as a citalopram-treated mother with CYP2C19 poor metabolizer status, but the serum drug levels of their infants were still either undetectable (paroxetine) or low (citalopram). There was no evidence of adverse events in the drug-exposed infants. Serum drug levels in breastfed infants of antidepressant-treated mothers were undetectable or low. This study adds further evidence to previously

published data indicating that breastfeeding should not be generally discouraged in women using serotonin reuptake inhibitor antidepressants.

CC 1-11 (Pharmacology)

IT **Mental disorder**

(postpartum **depression**; breastfeeding during maternal antidepressant treatment of postpartum **depression**, infant exposure, clin. symptoms, and cytochrome P 450 genotypes)

IT 54910-89-3, Fluoxetine 59729-33-8, Citalopram 61869-08-7, Paroxetine 79617-96-2, Sertraline 93413-69-5, Venlafaxine

RL: ADV (Adverse effect, including toxicity); PKT

(Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(breastfeeding during maternal antidepressant treatment of postpartum **depression**, infant exposure, clin. symptoms, and cytochrome P 450 genotypes)

REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 170 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2004:903321 HCAPLUS

DOCUMENT NUMBER: 142:190947

TITLE: A double-blind comparison of escitalopram and venlafaxine extended release in the treatment of major depressive disorder

AUTHOR(S): Bielski, Robert J.; Ventura, Daniel; Chang, Chung-Chi

CORPORATE SOURCE: Summit Research Network, Okemos, MI, USA

SOURCE: Journal of Clinical Psychiatry (2004), 65(9), 1190-1196

CODEN: JCLPDE; ISSN: 0160-6689

PUBLISHER: Physicians Postgraduate Press, Inc.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Escitalopram is the most selective serotonin reuptake inhibitor (SRI) antidepressant available. Venlafaxine is a nonselective SRI that also inhibits noradrenergic reuptake. This study compared escitalopram and venlafaxine extended release (XR) in depressed outpatients at the highest doses recommended in the United States. In this randomized trial, patients (diagnosis of DSM-IV-defined major depressive disorder; baseline Hamilton Rating Scale for Depression score of ≥ 20) received 1 wk of single-blind placebo treatment, followed by 8 wk of double-blind, fixed-dose treatment with either escitalopram or venlafaxine XR (rapidly titrated to 20 mg/day and 225 mg/day, resp., in accordance with prescribing information). The primary efficacy variable was change from baseline to week 8 in Montgomery-Asberg Depression Rating Scale (MADRS) total score. Data were collected from May to Dec. 2002. Mean baseline MADRS scores for the escitalopram (N = 97) and venlafaxine XR (N = 98) groups were 30.7 and 30.0, resp. There were no significant differences in measures of efficacy between the 2 antidepressants. Mean changes from baseline to endpoint in MADRS total score for escitalopram and venlafaxine XR were -15.9 and -13.6, resp. Remission (MADRS score of ≤ 10) rates at endpoint were 41.2% for escitalopram and 36.7% for venlafaxine XR. Response ($\geq 50\%$ reduction from baseline MADRS score) rates for the escitalopram and venlafaxine XR groups were 58.8% and 48.0%, resp. Tolerability measures favored escitalopram over venlafaxine XR treatment. The venlafaxine XR group had a higher incidence than the escitalopram group of treatment-emergent adverse events (85.0% vs. 68.4%) and discontinuation due to adverse events (16.0% vs. 4.1%; $p < .01$). Results of this study indicate that, when titrated rapidly to their maximum recommended doses, escitalopram is at least as effective as venlafaxine XR

and significantly better tolerated. These results do not support the hypothesis that nonselective SRIs have greater efficacy than selective SRIs.

CC 1-11 (Pharmacology)

IT **Mental disorder**

(major **depression**; escitalopram vs. venlafaxine extended release in treatment of major depressive disorder)

IT 93413-69-5, Venlafaxine 128196-01-0, Escitalopram

RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(escitalopram vs. venlafaxine extended release in treatment of major depressive disorder)

REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 171 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2005:68061 HCAPLUS

DOCUMENT NUMBER: 143:19759

TITLE: Antidepressant treatment and risk of suicide attempt by adolescent with major depressive disorder: a propensity-adjusted retrospective cohort study

AUTHOR(S): Valuck, Robert J.; Libby, Anne M.; Sills, Marion R.; Giese, Alexis A.; Allen, Richard R.

CORPORATE SOURCE: Department of Clinical Pharmacy, School of Pharmacy, University of Colorado, Denver, CO, USA

SOURCE: CNS Drugs (2004), 18(15), 1119-1132
CODEN: CNDREF; ISSN: 1172-7047

PUBLISHER: Adis International Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Context: The US FDA has issued an advisory warning of a possible link between antidepressant treatment for paediatric patients with major depressive disorder (MDD) and an increased risk of suicidal behavior. A large database of paid health insurance claims for adolescents with MDD provided the opportunity to examine this possible relationship. Objective: To examine the potential empirical link between antidepressant treatment and suicide attempts among adolescents aged 12-18 years using a community sample of managed care enrollees across the US. Design: A retrospective longitudinal cohort using paid insurance claims for all healthcare and prescription fills for adolescents who were newly diagnosed with MDD and had at least 6 mo of follow-up data. A multivariate Cox proportional hazards regression anal. was used to test the hypothesis that antidepressant use increased the risk of suicide attempt, adjusting for propensity for allocation to each treatment group and for demog. and clin. characteristics. Setting: Managed care plans including both com. and Medicaid plans in the east, midwest, south and western regions of the US from Jan. 1997 to Mar. 2003. Participants: All adolescent insurance members aged 12-18 years at first diagnosis of MDD. Main outcome measures: Suicide attempts as indicated by medical utilization with International Classification of Diseases (9th edition) [ICD-9] or 10th edition (ICD-10) codes in any healthcare setting or by any covered provider. Results: 24 119 adolescents met inclusion criteria (63% female). Crude suicide attempt rates ranged from 0.0-2.3% by index treatment group. Treatment with SSRIs ((hazard ratio) [HR] = 1.59; CI 0.89, 2.82), other antidepressants (HR = 1.03; CI 0.43, 2.44), or multiple antidepressants (HR = 1.43; CI 0.70, 2.89) after index MDD diagnosis resulted in no statistically increased risk of suicide attempt. Treatment with antidepressant medication for at least 180 days (6 mo) reduced the

likelihood of suicide attempt compared with antidepressant treatment for <55 days (8 wk) [HR = 0.34; CI 0.21, 0.55]. Other variables that were independently associated with greater risk of suicide attempts included female gender, severity of illness indicators, younger age at time of MDD diagnosis, and living in the midwest or west. Conclusions: Antidepressant medication use had no statistically significant effect on the likelihood of suicide attempt in a large cohort of adolescents across the US after propensity adjustment for treatment allocation and controlling for other factors. The relationship between suicidal behavior and antidepressant medication use is complex and requires further investigation.

CC 1-11 (Pharmacology)

IT **Mental disorder**

(major **depression**; antidepressants showed no significant association with suicide attempt in adolescent major depressive disorder patient)

IT 50-47-5, Desipramine 50-48-6, Amitriptyline 50-49-7, Imipramine 72-69-5, Nortriptyline 303-49-1, Clomipramine 1668-19-5, Doxepin 19794-93-5, Trazodone 34911-55-2, Bupropion 54739-18-3, Fluvoxamine 83366-66-9, Nefazodone 85650-52-8, Mirtazapine **93413-69-5**, Venlafaxine 128196-01-0, Escitalopram

RL: ADV (Adverse effect, including toxicity); **PAC (Pharmacological activity)**; **THU (Therapeutic use)**; BIOL (Biological study);

USES (Uses)

(venlafaxine selective serotonin reuptake inhibitor increased shares of index medication frequency and was not associated with suicide attempt in adolescent major **depressive** disorder patient)

REFERENCE COUNT: 64 THERE ARE 64 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 172 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2004:147351 HCAPLUS

DOCUMENT NUMBER: 141:253582

TITLE: Time course of clinical response to venlafaxine: relevance of plasma level and chirality

AUTHOR(S): Gex-Fabry, Marianne; Balant-Gorgia, Androniki E.; Balant, Luc P.; Rudaz, Serge; Veuthey, Jean-Luc; Bertschy, Gilles

CORPORATE SOURCE: Department of Psychiatry, Clinical Research Unit, Chene-Burg, 1225, Switz.

SOURCE: European Journal of Clinical Pharmacology (2004), 59(12), 883-891

CODEN: EJCPAS; ISSN: 0031-6970

PUBLISHER: Springer-Verlag

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Objective: Early clin. response to antidepressant treatment is an important therapeutic goal, considering the psychol., social and economic consequences of depression. The aim of the present study was to investigate the relationship between the time course of response and the concentration of venlafaxine (V), its active metabolite O-desmethylvenlafaxine (ODV) and enantiomeric ratios V(+)/V(-) and ODV(+)/ODV(-). Methods: Depressed inpatients (n=35) received V orally at a fixed 300 mg daily dose. Accepted comedication included clorazepate (maximum 60 mg/day), zopiclone (maximum 15 mg/day) and low-dose trazodone (maximum 200 mg/day). Severity of depression was assessed on days 0, 4, 7, 11, 14, 21 and 28 (Montgomery and Åsberg Depression Rating Scale). Blood samples were taken on day 14 and day 28 and submitted to stereoselective determination. All measurements reflected trough steady-state values. First, pattern anal. was used to provide a categorical perspective of clin. response (50%

improvement from baseline depression score). Patients displaying non-response, transient response, early persistent response and delayed persistent response were compared with respect to racemic concns. and enantiomeric ratios. Second, in a dimensional perspective, mixed-effects modeling was used to analyze severity of depression vs. time curves with respect to the possible influence of concns. and enantiomeric ratios. Results: Comparison of patients with and without persistent response did not reveal any significant difference for V, ODV, V+ODV plasma levels or enantiomeric ratios. Persistent response was significantly associated with less frequent pre-study antidepressant medication and less frequent comedication with zopiclone (day 14) and clorazepate (day 28) during the study. Focus on patients with persistent response (n=19, 54.3%) indicated that early response, first observed before day 14, was associated with significantly higher V+ODV concentration than delayed response (median 725 ng/mL

vs. 554 ng/mL, P=0.023). No difference was found for pre-study medication or comedication during the study. Shorter time to onset of response was significantly associated with lower V(+)/V(-) enantiomeric ratio (rs=0.48, P<0.05). Mixed-effects modeling of depression severity vs. time curves in patients with persistent response confirmed that either higher V+ODV plasma level or lower V(+)/V(-) ratio were significantly associated with more rapid decrease of depression score (likelihood ratio tests, P=0.012 and P=0.046, resp.). Conclusion: Considering its modest sample size, naturalistic design and limited observation period, the present study provided preliminary indication that earlier clin. response may occur with higher V+ODV plasma level, extending previous dose-response studies. The hypothesis was also raised that exposure to a more potent noradrenergic therapeutic moiety, as reflected by a lower V(+)/V(-) ratio, may be relevant to early improvement of depression.

CC 1-2 (Pharmacology)

IT **Mental disorder**

(**depression**; earlier clin. response and more rapid decrease of **depression** score was associated with either higher plasma concentration of V and ODV or lower V(+)/(V-) ratio in **depression** patient receiving venlafaxine)

IT 93413-69-5, Venlafaxine

RL: PAC (Pharmacological activity); PKT

(Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(earlier clin. response and more rapid decrease of **depression** score was associated with either higher plasma concentration of V and ODV or lower V(+)/(V-) ratio in **depression** patient receiving venlafaxine)

REFERENCE COUNT: 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 173 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2004:618136 HCAPLUS

DOCUMENT NUMBER: 141:200021

TITLE: A comparative study of milnacipran and imipramine in the treatment of major depressive disorder

AUTHOR(S): Lopez-Ibor, J. J.; Conesa, A.

CORPORATE SOURCE: The Spanish Milnacipran/Imipramine Study Group, Hospital Ramon Y Cajal, Madrid, Spain

SOURCE: Current Medical Research and Opinion (2004), 20(6), 855-860

CODEN: CMROCX; ISSN: 0300-7995

PUBLISHER: LibraPharm Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The antidepressant efficacy and safety of milnacipran, a dual action antidepressant drug which inhibits the reuptake of serotonin and noradrenaline, was compared with that of the tricyclic antidepressant, imipramine, in a multicentre, double-blind, randomised, parallel group, comparative trial in 5 hospital centers in Spain. One hundred patients hospitalised with a diagnosis of major depressive disorder according to the Diagnostic and Statistical Manual of the American Psychiatry Association (third revision), with a min. score of 25 on the Montgomery and Asberg Depression Rating Scale were treated for 6 wk with milnacipran (100 mg/day) or imipramine (150 mg/day). Both treatments showed similar efficacy in reducing depressive symptoms. The frequency of most adverse events in the milnacipran-treated patients was lower than that observed in the imipramine group, particularly those related to anticholinergic symptoms. Dysuria and shivering, however, were more common with milnacipran. The results of this study support others which have demonstrated that milnacipran has equivalent efficacy but superior tolerability to a tricyclic antidepressant such as imipramine.

CC 1-11 (Pharmacology)

IT **Mental disorder**

(major **depression**; milnacipran vs. imipramine in the treatment of major depressive disorder)

IT 50-49-7, Imipramine 92623-85-3, Milnacipran

RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study);

USES (Uses)

(milnacipran vs. imipramine in the treatment of major depressive disorder)

REFERENCE COUNT: 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 174 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2004:1047534 HCAPLUS

DOCUMENT NUMBER: 142:384746

TITLE: Duloxetine: A new serotonin/noradrenaline reuptake inhibitor for the treatment of depression

AUTHOR(S): Rabasseda, Xavier

CORPORATE SOURCE: Medical Information Department, Prous Science, Barcelona, Spain

SOURCE: Drugs of Today (2004), 40(9), 773-790
CODEN: MDACAP; ISSN: 0025-7656

PUBLISHER: Prous Science

DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

AB A review. Double-blind, placebo-controlled clin. trials have evaluated and demonstrated the efficacy of duloxetine as an antidepressant in patients with major depressive disorders. The drug has been noted to be well tolerated and effective in the control of depressive symptoms. In addition, duloxetine has been shown to be better than placebo and as effective as paroxetine as an **antidepressant** and also better than placebo for reducing **pain** in both exptl. models and patients. Duloxetine is a safe and well-tolerated new treatment option for **depression** including anxiety and **painful** phys. symptoms. Furthermore, duloxetine has proven robust efficacy in stress urinary incontinence.

CC 1-0 (Pharmacology)

IT **Mental disorder**

(**depression**; serotonin/noradrenaline reuptake inhibitor duloxetine for treatment of **depression**)

IT **Nervous system agents**
(noradrenaline reuptake inhibitors;
serotonin/noradrenaline reuptake inhibitor duloxetine for treatment of
depression)
IT **116539-59-4, Duloxetine**
RL: ADV (Adverse effect, including toxicity); **DMA (Drug mechanism of
action); PAC (Pharmacological activity); PKT**
(Pharmacokinetics); **THU (Therapeutic use); BIOL (Biological
study); USES (Uses)**
(serotonin/noradrenaline reuptake inhibitor duloxetine for treatment of
depression)

REFERENCE COUNT: 120 THERE ARE 120 CITED REFERENCES AVAILABLE FOR
THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE
FORMAT

L91 ANSWER 175 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:959433 HCAPLUS
DOCUMENT NUMBER: 142:233036
TITLE: Venlafaxine for the Treatment of Depressive Episode
During the Course of Schizophrenia
AUTHOR(S): Mazeh, Doron; Shahal, Baruch; Saraf, Roni; Melamed,
Yuval
CORPORATE SOURCE: Abarbanel Mental Health Center, Bat-Yam and Sackler
Sch Med, Tel-Aviv University, Tel-Aviv, Israel
SOURCE: Journal of Clinical Psychopharmacology (2004), 24(6),
653-655
CODEN: JCPYDR; ISSN: 0271-0749
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The emergence of depression in the course of schizophrenia is common and
arouses much interest and therapeutic concern. It has been associated with a
less favorable prognosis and increased incidence of suicide. However,
relatively few treatment studies have been performed in this area. The
use of a combination of antidepressants and antipsychotic agents is
controversial. We report an open-label study carried out to evaluate the
efficacy of the addition of venlafaxine in schizophrenia patients treated
with antipsychotics and diagnosed with concurrent depressive episode
(Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
criteria). Patients (N = 19) who did not show spontaneous improvement
after 4 wk were assigned to a 6-wk trial with add-on venlafaxine.
Patients were evaluated at a 1-wk interval with the Hamilton Depressive
Rating Scale, the Pos. and Neg. Syndrome Scale, and the Clin. Global
Impression Scale. All 19 patients had completed the 6-wk trial. Fourteen
patients (74%) showed significant improvement measured with Hamilton
Depressive Rating Scale and Clin. Global Impression Scale. The mean
venlafaxine dose was 146 mg/d (range: 75 to 225 mg/d). In most patients,
there was a parallel decrease in psychotic symptoms. We conclude that
venlafaxine may have a role in the treatment of depression in patients
with schizophrenia without causing exacerbation of psychosis.

CC 1-11 (Pharmacology)

IT **Mental disorder**
(depression; venlafaxine can be used for treatment of
depression without exacerbating psychosis in schizophrenic
patient treated with antipsychotics)

IT **93413-69-5, Venlafaxine**
RL: ADV (Adverse effect, including toxicity); **PAC (Pharmacological
activity); THU (Therapeutic use); BIOL (Biological study);**
USES (Uses)

(venlafaxine can be used for treatment of **depression** without exacerbating psychosis in schizophrenic patient treated with antipsychotics)

REFERENCE COUNT: 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 176 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2005:56547 HCAPLUS

DOCUMENT NUMBER: 142:441669

TITLE: Post-treatment emergent adverse events in depressed patients following treatment with milnacipran and paroxetine

AUTHOR(S): Vandel, P.; Sechter, D.; Weiller, E.; Pezous, N.; Cabanac, F.; Tournoux, A.

CORPORATE SOURCE: Service de Psychiatrie et Psychologie Medicale, CHU St Jacques, Besancon, Fr.

SOURCE: Human Psychopharmacology (2004), 19(8), 585-586
CODEN: HUPSEC; ISSN: 0885-6222

PUBLISHER: John Wiley & Sons Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The results of an anal. of post-treatment adverse events resulting from paroxetine and milnacipran withdrawals of patients suffering from major depression episodes are discussed. Under identical double-blind conditions at equally EDs, paroxetine produced systematically more post-treatment emergent adverse events than milnacipran. In addition, the qual. nature of the adverse events differed between the two drugs with dizziness, anxiety, and sleep disturbance (insomnia and nightmares) as the principal effects occurring with paroxetine while anxiety was the major effect reported with milnacipran. The reason for this difference is not clear but it may relate to the dual action of milnacipran on the reuptake of noradrenaline and serotonin compared with the selective effect of paroxetine on the reuptake of serotonin. These results underline the importance of gradually tapering any antidepressant therapy at the end of treatment, especially with paroxetine.

CC 1-11 (Pharmacology)

IT **Mental disorder**

(**depression**; post-treatment emergent adverse events in depressed patients following treatment with milnacipran and paroxetine)

IT 61869-08-7, Paroxetine 92623-85-3, Milnacipran

RL: ADV (Adverse effect, including toxicity); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)

(post-treatment emergent adverse events in **depressed** patients following treatment with milnacipran and paroxetine)

REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 177 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2005:68165 HCAPLUS

DOCUMENT NUMBER: 143:19763

TITLE: Combination therapy with venlafaxine and carbamazepine in depressive patients not responding to venlafaxine: pharmacokinetic and clinical aspects

AUTHOR(S): Ciusani, Elio; Zullino, Daniele F.; Eap, Chin B.; Brawand-Amey, Marlyse; Brocard, Murielle; Baumann, Pierre

CORPORATE SOURCE: Unite de Biochimie et Psychopharmacologie Clinique, Departement Universitaire de Psychiatrie Adulte, Prilly-Lausanne, Switz.

SOURCE: Journal of Psychopharmacology (London, United Kingdom)
(2004), 18(4), 559-566
CODEN: JOPSEQ; ISSN: 0269-8811
PUBLISHER: Sage Publications Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The chiral antidepressant venlafaxine (VEN) is both a serotonin and a norepinephrine uptake inhibitor. CYP2D6 and CYP3A4 contribute to its metabolism, which has been shown to be stereoselective. Ten CYP2D6 genotyped and depressive (F32x and F33x, ICD-10) patients participated in an open study on the pharmacokinetic and pharmacodynamic consequences of a carbamazepine augmentation in VEN non-responders. After an initial 4-wk treatment with VEN (195 ± 52 mg/day), the only poor metabolizer out of 10 depressive patients had the highest plasma concns. of S-VEN and R-VEN, resp., whereas those of R-O-dimethyl-VEN were lowest. Five non-responders completed the second 4-wk study period, during which they were submitted to a combined VEN-carbamazepine treatment. In the only non-responder to this combined treatment, there was a dramatic decrease of both enantiomers of VEN, O-dimethylvenlafaxine, N-desmethylvenlafaxine and N,O-didesmethylvenlafaxine in plasma, which suggests non-compliance, although metabolic induction by carbamazepine cannot entirely be excluded. The administration of carbamazepine [mean ± SD, range: 360 ± 89 (200-400) mg/day] over 4 wk did not result in a significant modification of the plasma concns. of the enantiomers of VEN and its O- and N-demethylated metabolites in the other patients. In conclusion, these preliminary observations suggest that the combination of VEN and carbamazepine represents an interesting augmentation strategy by its efficacy, tolerance and absence of pharmacokinetic modifications. However, these findings should be verified in a more comprehensive study.

CC 1-11 (Pharmacology)

IT **Mental disorder**

(**depression**; carbamazepine did not affect pharmacokinetics of VEN enantiomers and its metabolites suggests combination therapy with carbamazepine and venlafaxine may be effective and safe treatment in depressive patients not responding to venlafaxine)

IT 93413-69-5, Venlafaxine

RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(carbamazepine did not affect pharmacokinetics of venlafaxine enantiomers and its metabolites suggests combination therapy with carbamazepine and VEN may be effective and safe treatment in depressive patients not responding to venlafaxine)

REFERENCE COUNT: 47 THERE ARE 47 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 178 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2004:477663 HCAPLUS

DOCUMENT NUMBER: 141:82181

TITLE: The effect of duloxetine on painful physical symptoms in depressed patients: do improvements in these symptoms result in higher remission rates?

AUTHOR(S): Fava, Maurizio; Mallinckrodt, Craig H.; Detke, Michael J.; Watkin, John G.; Phil, D.; Wohlreich, Madelaine M.

CORPORATE SOURCE: Department of Psychiatry, Massachusetts General Hospital, Boston, USA

SOURCE: Journal of Clinical Psychiatry (2004), 65(4), 521-530
CODEN: JCLPDE; ISSN: 0160-6689

PUBLISHER: Physicians Postgraduate Press, Inc.

DOCUMENT TYPE: Journal
LANGUAGE: English

AB Background: Depression is a chronic disease consisting of emotional/psychol. and phys. symptoms. Emotional symptoms have been shown to respond to currently available antidepressants; however, phys. symptoms may not be as responsive. It was hypothesized that resolution of both psychol. and phys. symptoms of depression would predict a higher percentage of patients achieving remission. Method: Efficacy data were pooled from 2 identical, but independent, 9-wk randomized, double-blind clin. trials of duloxetine 60 mg q.d. (N = 251) and placebo (N = 261). All patients met diagnostic criteria for DSM-IV major depressive disorder, which was confirmed by the Mini-International Neuropsychiatric Interview. Efficacy measures included the 17-item Hamilton Rating Scale for Depression (HAM-D-17) total score, the HAM-D-17 Maier subscale, the Clin. Global Impressions-Severity of Illness (CGI-S) scale, the Patient Global Impression of Improvement (PGI-I) scale, the Somatic Symptom Inventory, the Quality of Life in Depression Scale, and Visual Analog Scales (VAS) for pain (overall pain, headaches, back pain, shoulder pain, interference with daily activities, and time in pain while awake). Results: Duloxetine-treated patients demonstrated significantly greater improvement in overall pain ($p = .016$), back pain ($p = .002$), and shoulder pain ($p = .021$) at week 9 compared with patients receiving placebo. When treatment effects were pooled over all visits, patients receiving duloxetine, 60 mg q.d., exhibited significantly greater improvement than placebo-treated patients in 5 of the 6 assessed VAS pain measures. Approx. 50% of the improvement in overall pain was independent of improvement in HAM-D-17 total score. Assuming the same level of improvement in core emotional symptoms of depression (Maier subscale), improvement in overall pain severity was associated with higher estimated probabilities of remission ($p < .001$). The week 9 means for VAS overall pain severity were 13.0 for remitters (last observed value for HAM-D-17 was ≤ 7) compared with 22.7 for nonremitters ($p < .001$), resp., representing a greater than 3-fold improvement from baseline in remitters. The remission rate for pain responders (improvement in VAS overall pain from baseline to last observation $> 50\%$) was twice that observed for pain nonresponders (36.2% vs. 17.8%, $p < .001$). Greater improvements in pain outcomes were associated with more favorable end-point outcomes on the CGI-S and PGI-I scales. In addition, early favorable responses in VAS overall pain severity were associated

with favorable endpoint outcomes. Conclusions: Treatment with duloxetine, 60 mg q.d., significantly reduced pain compared with placebo. Improvements in pain severity were attributable equally to the direct effect of duloxetine and to associated changes in depression severity. Improvement in painful phys. symptoms was associated with higher remission rates even after accounting for improvement in core emotional symptoms.

CC 1-11 (Pharmacology)

IT **Mental disorder**

(depression; duloxetine effect on painful phys. symptoms in depressed patients)

IT 116539-59-4, Duloxetine

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(duloxetine effect on painful phys. symptoms in depressed patients)

REFERENCE COUNT: 55 THERE ARE 55 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 179 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2004:727908 HCAPLUS

DOCUMENT NUMBER: 142:49054
TITLE: Cost and Effectiveness of Venlafaxine Extended-Release and Selective Serotonin Reuptake Inhibitors in the Acute Phase of Outpatient Treatment for Major Depressive Disorder
AUTHOR(S): Trivedi, Madhukar H.; Wan, George J.; Mallick, Rajiv; Chen, Jiuling; Casciano, Roman; Geissler, Erika C.; Panish, Jessica M.
CORPORATE SOURCE: University of Texas Southwestern Medical Center, Dallas, TX, USA
SOURCE: Journal of Clinical Psychopharmacology (2004), 24(5), 497-506
CODEN: JCPYDR; ISSN: 0271-0749
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The purpose of this retrospective anal. was to estimate the cost and effectiveness of venlafaxine extended-release (VXR) compared with selective serotonin reuptake inhibitors in the outpatient treatment of major depressive disorder. A decision modeling approach was used to determine cost and effectiveness ratios. Patients on VXR were associated with 22.8 depression-free days vs. 18.6 depression-free days with the studied selective serotonin reuptake inhibitors, based on the decision model. Productive and quality-adjusted days were also expected to increase for VXR patients (22.06 vs. 19.34 and 4.56 to 9.36 vs. 3.72 to 7.63), as was the percentage of patients achieving full activity (25.9% vs. 19.6%). The expected cost per patient achieving remission of symptoms was US1303.94 and US1514.96, and the cost per depression-free days was US25.66 and US28.25, for the VXR and selective serotonin reuptake inhibitors groups, resp. Treatment with VXR is not only expected to increase the rate of remission of symptoms but is also associated with achievement of full activity, higher number of depression-free days, productive days, and quality-adjusted days. VXR is a cost-effective treatment option for major depressive disorder.
CC 1-11 (Pharmacology)
IT **Mental disorder**
(major depression; cost and effectiveness of venlafaxine ERand SSRIs in patients with major depressive disorder)
IT 54739-18-3, Fluvoxamine 54910-89-3, Fluoxetine 61869-08-7, Paroxetine 93413-69-5, Venlafaxine
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study);
USES (Uses)
(cost and effectiveness of venlafaxine ERand SSRIs in patients with major depressive disorder)
REFERENCE COUNT: 63 THERE ARE 63 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT
L91 ANSWER 180 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:156299 HCAPLUS
DOCUMENT NUMBER: 140:297362
TITLE: Proteomic analysis of protein changes developing in rat hippocampus after chronic antidepressant treatment: Implications for depressive disorders and future therapies
AUTHOR(S): Khawaja, Xavier; Xu, Jun; Liang, Jin-Jun; Barrett, James E.
CORPORATE SOURCE: Wyeth Neuroscience, Princeton, NJ, USA
SOURCE: Journal of Neuroscience Research (2004), 75(4),

451-460

CODEN: JNREDK; ISSN: 0360-4012

PUBLISHER: Wiley-Liss, Inc.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB It is recognized that monoamine reuptake inhibitors (MARIs) exert beneficial effects in the treatment of major depression and general anxiety disorder. The aim of this study was to identify proteins regulated by this class of antidepressant using a proteome differential profiling approach. Either venlafaxine or fluoxetine was administered systemically to adult rats for 2 wk, and protein patterns from rat hippocampal cytosolic exts. were compared by two-dimensional gel electrophoresis. Silver-stained protein spots displaying differential expression were identified by mass spectrometry. Thirty-three protein spots were modulated by both drug treatments compared to controls. The classification of several proteins that were sorted by function suggested convergent pathway activities for both MARIs at the post-receptor level. These included proteins associated with neurogenesis (insulin like growth factor 1 (IGF-1), glia maturation factor [GMF]- β), outgrowth/maintenance of neuronal processes (hippocampal cholinergic neurostimulating peptide [HCNP], PCTAIRE-3), and with neural regeneration/axonal guidance collapsing response mediator protein (CRMP-2) systems. Other modulated proteins indicated an increase in neuronal vesicular cell trafficking and synaptic plasticity (Ras-related protein 4a (Rab 4a), Ras-related protein 1b (Rab 1b), heat shock protein 10 [HSP10]), as well as neurosteroidogenic (hydroxysteroid sulfotransferase A) and possible anti-apoptotic (dimethylargininase-1 L-N,N-dimethylarginine dimethylaminohydrolase-1 [DDAH-1], pyruvate dehydrogenase-E1 [PDH-E1], antioxidant protein-2 [AOP-2]) pathway-mediated regulatory events. Parallel studies to investigate further the effects of venlafaxine and fluoxetine on adult hippocampal neurogenesis in vivo by quant. bromodeoxyuridine immunolabeling revealed a significant drug-induced increase in the proliferation rate and long-term survivability of progenitor stem cells located in the subgranular zone. These data suggest that MARIs share wide-ranging proteome changes within the hippocampal formation, beyond 5-HT/NE neurotransmission. This may reflect long-term functional adaptations required for antidepressant activity.

CC 1-11 (Pharmacology)

IT **Mental disorder**

(**depression**; proteomic anal. of protein changes developing in rat hippocampus after chronic antidepressant treatment: implications for depressive disorders and future therapies)

IT 54910-89-3, Fluoxetine 93413-69-5, Venlafaxine

RL: **PAC (Pharmacological activity)**; BIOL (Biological study)

(proteomic anal. of protein changes developing in rat hippocampus after chronic antidepressant treatment: implications for **depressive** disorders and future therapies)

REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 181 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2004:796232 HCAPLUS

DOCUMENT NUMBER: 142:86467

TITLE: Differential effects of fluvoxamine, paroxetine and milnacipran for depression, especially with regard to age

AUTHOR(S): Morishita, Shigeru; Arita, Seizaburo

CORPORATE SOURCE: Depression Prevention Medical Center, Kyoto Jujo Hospital, Kyoto, Japan

SOURCE: Human Psychopharmacology (2004), 19(6), 405-408
CODEN: HUPSEC; ISSN: 0885-6222
PUBLISHER: John Wiley & Sons Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Selective serotonin reuptake inhibitors (SSRIs) and dual serotonin and noradrenaline reuptake inhibitors (SNRIs) are the most commonly prescribed classes of antidepressants, yet it is not known whether one is superior to the other. It seems that an investigation of the characteristics of patients being treated with SSRIs and SNRIs would be useful in determining which patients would be most likely to benefit from these antidepressant medications. The purpose of this retrospective study was to compare the response to fluvoxamine, paroxetine and milnacipran treatment for depression with regard to patient age. A retrospective cohort anal. was carried out among depression outpatients treated in the Department of Psychiatry, Kawasaki Medical School Hospital, Kurashiki, Japan, in 2001. A total of 159 patients who met the criteria and who were receiving fluvoxamine, paroxetine and milnacipran were identified. To examine the influence of antidepressants with regard to patient age, the response rate of patients aged 50 yr or older was compared with that of those aged 49 yr or younger. In patients aged 49 yr or younger, the clin. effect of fluvoxamine was greater than that of the other antidepressants. Conversely, in those aged 50 yr or older, milnacipran had a tendency to be more effective than the others. The differential response of SSRIs and SNRIs with regard to age should help to guide clinicians in determining the selection of antidepressants for depression.
CC 1-11 (Pharmacology)
IT **Mental disorder**
(depression; differential effects of fluvoxamine, paroxetine and milnacipran for depression, especially with regard to age)
IT 54739-18-3, Fluvoxamine 61869-08-7, Paroxetine 92623-85-3, Milnacipran
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(differential effects of fluvoxamine, paroxetine and milnacipran for depression, especially with regard to age)
REFERENCE COUNT: 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 182 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:405483 HCAPLUS
DOCUMENT NUMBER: 141:46638
TITLE: Older adults
AUTHOR(S): Glover, S.; Boyer, W. F.
CORPORATE SOURCE: VAMC Atlanta, Decatur, GA, 30033-4004, USA
SOURCE: Handbook of Experimental Pharmacology (2004), 157(Antidepressants), 393-420
CODEN: HEPHD2; ISSN: 0171-2004
PUBLISHER: Springer-Verlag
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. Depression in the elderly is a major public health problem associated with increased morbidity, mortality, functional impairment, and a diminished quality of life. Unfortunately, late-life depression often goes unrecognized and untreated. Healthy, ambulatory elderly patients can often be treated in the same way as younger patients, whereas frail elderly patients (usually the "old" old) often need to be approached more conservatively, with special attention to phys. status and concomitant

illnesses. Clinicians should also consider the patient's environment (e.g., whether living at home or in a nursing home). Elderly patients may underreport psychol. symptoms and overreport somatic symptoms (e.g., pain); collateral histories from families, friends, or professional caregivers are invaluable aids in diagnosis. Secondary depressions are also common in the elderly, since numerous medical disorders, medications, and life stresses can lead to depressive syndromes. Before initiating antidepressant treatment, clinicians should screen for and treat any concurrent medical condition(s), provide psychol. support for the patient, identify and provide assistance with social or economic difficulties, and involve the patient's family or support network. Social and psychol. supportive approaches should preferably precede pharmacol. management in mild or stable cases. Some elderly patients respond well to traditional or time-limited psychotherapies, cognitive-behavioral interventions, or spiritual support in individual or group settings. The ideal antidepressant agent for elderly patients should not cause orthostasis or cardiotoxicity and should cause little sedation or impairment of phys. and cognitive abilities. Although data are inconsistent as to whether elderly patients are more likely to develop side effects than younger patients, the aged often do not tolerate side effects as well. Clinicians should take into account the heterogeneity of the elderly population in pharmacokinetic and pharmacodynamic parameters and practice individualized titration of all medications coupled with therapeutic drug monitoring. In general, the rule of "start low, go slow" applies, except when rapid symptom relief is of paramount importance. The SSRIs are important agents for the treatment of depression in the elderly, given their tolerability, wide therapeutic index and efficacy. The tricyclic antidepressants are efficacious in treating depression in the elderly. The secondary amines (e.g., desipramine, nortriptyline) are preferred over the tertiary amines (e.g., amitriptyline and imipramine) because they cause fewer serious side effects. Therapeutic drug monitoring is recommended in using TCAs in older patients, and clinicians should be alert for the risk of drug-drug interactions since many older patients are taking multiple medications. A number of other antidepressants have been shown to be effective and well tolerated in elderly depressed patients, including reboxetine, venlafaxine, and bupropion. In treating more severe depressive illness consideration should be given to ECT or prescribing a TCA or venlafaxine because of possibly increased response rates with these agents. Elderly patients who do not respond adequately to antidepressant monotherapy should be considered for antidepressant combinations or augmentation with lithium, thyroid, or hormone replacement (in perimenopausal depression). The appropriate duration of maintenance antidepressant medication will depend on the patient's history of depressive episodes.

CC 1-0 (Pharmacology)

IT **Mental disorder**

(depression; antidepressants in older adults with depressions)

IT 50-47-5, Desipramine 50-48-6, Amitriptyline 50-49-7, Imipramine
72-69-5, Nortriptyline 34911-55-2, Bupropion 71620-89-8, Reboxetine
93413-69-5, Venlafaxine

RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(antidepressants in older adults with depressions)

REFERENCE COUNT: 121 THERE ARE 121 CITED REFERENCES AVAILABLE FOR
THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE
FORMAT

L91 ANSWER 183 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2004:611722 HCAPLUS
 DOCUMENT NUMBER: 142:147770
 TITLE: Impact of polymorphisms of cytochrome-P450 isoenzymes 2C9, 2C19 and 2D6 on plasma concentrations and clinical effects of antidepressants in a naturalistic clinical setting
 AUTHOR(S): Grasmaeder, Katja; Verwohlt, Petra Louise; Rietschel, Marcella; Dragicevic, Aleksandra; Mueller, Matthias; Hiemke, Christoph; Freymann, Nikolaus; Zobel, Astrid; Maier, Wolfgang; Rao, Marie Luise
 CORPORATE SOURCE: Department of Psychiatry, University of Bonn, Bonn, 53105, Germany
 SOURCE: European Journal of Clinical Pharmacology (2004), 60(5), 329-336
 CODEN: EJCPAS; ISSN: 0031-6970
 PUBLISHER: Springer GmbH
 DOCUMENT TYPE: Journal
 LANGUAGE: English

AB Objective. This evaluation focuses on polymorphisms of the cytochrome-P 450 (CYP) isoenzymes 2C9, 2C19 and 2D6 and their association with plasma concns. within a typical clin. setting. Side effects and treatment response were analyzed in an exploratory approach in poor and ultra-rapid metabolizers. Patients and methods. We analyzed 136 Caucasian depressed inpatients treated with amitriptyline, citalopram, clomipramine, doxepin, fluvoxamine, mirtazapine, paroxetine, sertraline and venlafaxine, who underwent weekly plasma concentration measurements, assessment of the severity of illness and side effects during their stay in the hospital. Patients were genotyped with respect to CYP2C9 alleles *1 and *2, the CYP2C19 alleles *1, *2 and *3 and the CYP2D6 alleles *1 to *9 and CYP2D6 gene duplication. Results. CYP2D6 poor metabolizer genotype and co-medication with inhibitors of CYP2D6 were associated with higher plasma concns. than the drug-specific median plasma concentration when normalized to dose; plasma concns. of CYP2C19 extensive metabolizers and smokers were significantly lower than the drug-specific median. Five of the six CYP2D6 poor metabolizers experienced side effects. Response was not associated with plasma concns. above or below the lower limit of a presumed therapeutic range. Conclusion. These data indicate a significant influence of the CYP2D6 genotype, minor influence of the CYP2C19 genotype and no influence of the CYP2C9 genotype on plasma concns. of patients taking mainly second-generation antidepressants. Because of the good tolerability of the latter and the flat dose-response relationship, genotyping should only be considered in cases of suspected side effects.

CC 1-2 (Pharmacology)
 IT **Mental disorder**
 (depression; CYP2D6 genotype showed significant influence while CYP2C19 possessed minor influence and CYP2C9 had no influence on plasma concentration of drug in depressed patient receiving antidepressant drugs)

IT 93413-69-5, Venlafaxine
 RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (CYP2D6 genotype showed significant influence while CYP2C19 possessed minor influence and CYP2C9 had no influence on plasma concentration of drug in depressed patient receiving antidepressant therapy with venlafaxine)

REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 184 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2004:387676 HCAPLUS

DOCUMENT NUMBER: 141:33639

TITLE: Venlafaxine versus placebo in the preventive treatment
of recurrent major depression

AUTHOR(S): Montgomery, Stuart A.; Entsuah, Richard; Hackett,
David; Kunz, Nadia R.; Rudolph, Richard L.

CORPORATE SOURCE: Venlafaxine 335 Study Group, Imperial College School
of Medicine, London, UK

SOURCE: Journal of Clinical Psychiatry (2004), 65(3), 328-336
CODEN: JCLPDE; ISSN: 0160-6689

PUBLISHER: Physicians Postgraduate Press, Inc.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Background: Major depression is often chronic and recurrent, yet most
long-term therapeutic trials are not adequately designed to assess
antidepressant efficacy in recurrence prevention. Long-term efficacy and
safety of prophylactic venlafaxine treatment were evaluated in outpatients
with recurrent major depression. Method: Patients with a history of
recurrent DSM-III-R major depression received open-label treatment with
venlafaxine, 100 to 200 mg/day, for 6 mo. Those who responded to
treatment (Hamilton Rating Scale for Depression [HAM-D21] score \leq
12, day 56) and remained relapse-free (no more than 2 HAM-D21 scores $>$ 10
and no Clin. Global Impressions-Severity of Illness [CGI-S] score \geq
4, months 2-6) either continued taking venlafaxine, 100 to 200 mg/day, or
were switched in a double-blind fashion to placebo for 12 mo. The primary
efficacy outcome was the number of patients experiencing a recurrence of
major depression (CGI-S score \geq 4). The cumulative probability of
recurrence was calculated using the Kaplan-Meier method of survival anal.
Data were collected from Nov. 1992 through Dec. 1995. Results: Of the 235
patients who enrolled in the recurrence-prevention period, 225 (N = 109,
venlafaxine; N = 116, placebo) provided efficacy data. Survival anal.
determined a 22% cumulative probability of recurrence in venlafaxine-treated
patients after 12 mo compared with 55% for the placebo group ($p < .001$).
More than twice as many placebo-treated patients (48%) as
venlafaxine-treated patients (21%) discontinued treatment because of lack
of efficacy ($p < .001$). Conclusion: Twelve-month maintenance venlafaxine
treatment was significantly more efficacious than placebo in preventing
major depression recurrence in patients who had been successfully treated
with venlafaxine for 6 mo.

CC 1-11 (Pharmacology)

IT **Mental disorder**

(major depression; efficacy of venlafaxine in preventive
treatment of recurrent major depression)

IT 93413-69-5, Venlafaxine

RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological
activity); THU (Therapeutic use); BIOL (Biological study);

USES (Uses)

(efficacy of venlafaxine in preventive treatment of recurrent major
depression)

REFERENCE COUNT: 59 THERE ARE 59 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 185 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2004:682104 HCAPLUS

DOCUMENT NUMBER: 141:254340

TITLE: Subjective and polysomnographic effects of milnacipran on sleep in depressed patients
AUTHOR(S): Lemoine, Patrick; Faivre, Thierry
CORPORATE SOURCE: Biological Psychiatry Clinical Unit, Hopital du Vinatier, Lyon Bron, 69500, Fr.
SOURCE: Human Psychopharmacology (2004), 19(5), 299-303
CODEN: HUPSEC; ISSN: 0885-6222
PUBLISHER: John Wiley & Sons Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The effects of milnacipran (50 mg bid) on sleep patterns of eight depressed inpatients, treated for 4 wk, were studied during the initial (days 1-3) and terminal (days 26-28) treatment periods and compared with those obtained from three sleep recordings performed just prior to the initiation of the treatment. The clin. evolution of patients was evaluated weekly using the MADRS depression scale and the Spiegel and Norris sleep scales. Clin. improvement, shown by a mean reduction of 58% in MADRS scale scores, was accompanied by an improvement of disturbed sleep parameters. From the beginning of treatment, there was an increase in the total duration of sleep and stage II sleep, a decrease in sleep latency and an increase in sleep efficiency. Total REM sleep was not modified although, since there was an increase in total sleep time, the percent REM sleep was significantly reduced. REM latency was increased early in the study, an effect classically associated with antidepressant treatment. This study suggests that milnacipran improves disturbed sleep parameters in depressed patients without any addnl. disturbance at the onset of treatment.
CC 1-11 (Pharmacology)
IT **Mental disorder**
(depression; subjective and polysomnog. effects of milnacipran on sleep in depressed patients)
IT 92623-85-3, Milnacipran
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(subjective and polysomnog. effects of milnacipran on sleep in depressed patients)

REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 186 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2005:204910 HCAPLUS
DOCUMENT NUMBER: 142:385808
TITLE: The effectiveness of lithium augmentation of milnacipran: preliminary data using the modified Japanese psychopharmacology algorithm
AUTHOR(S): Kobayashi, Nobuhisa; Sawamura, Takehito; Yoshida, Takeshi; Yoshino, Aihide; Nomura, Soichiro
CORPORATE SOURCE: Dep. of Psychiatry, National Defense Medical College, Tokorozawa, Saitama, 359-8513, Japan
SOURCE: Nippon Shinkei, Seishin Yakurigaku Zasshi (2004), 24(5), 279-281
CODEN: NSSZEW; ISSN: 1340-2544
PUBLISHER: Nippon Shinkei Seishin Yakuri Gakkai
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Medication algorithms based on the best evidence available together with expert consensus are considered to promote logical consistent clin. decision making in the choice of antidepressant drugs. We report our preliminary results using the modified algorithm established by the

Japanese Psychopharmacol. Algorithm Project (JPAP). Subjects were 24 patients with major depressive disorders who presented to the outpatient clinic of the Department of Psychiatry at the National Defense Medical College prior to any treatment for the current episode. Ultimately, 15 patients recovered with treatment according to our protocol, including 7 who recovered upon treatment with first-line drugs; the most effective of these was paroxetine, followed by fluvoxamine and then milnacipran. Six patients recovered with second-line treatments. Among these, a combination of milnacipran and lithium was most effective, with recovery of 4 of 4 patients. We have formed a strong impression that augmentation therapy, especially with milnacipran plus lithium, is likely to be effective if the first-line antidepressant is ineffective. Investigation of more cases will be needed to confirm or refine details of the algorithm and, more generally, to determine the best approach to antidepressant medication.

CC 1-11 (Pharmacology)

IT **Mental disorder**

(depression; paroxetine effective as first-line therapy than fluvoxamine, milnacipran, milnacipran + lithium effective as second-line therapy in depressive disorder patient suggest milnacipran + lithium likely effective if first-line therapy ineffective)

IT 7439-93-2, Lithium, biological studies 54739-18-3, Fluvoxamine
61869-08-7, Paroxetine 92623-85-3, Milnacipran

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(paroxetine effective as first-line therapy than fluvoxamine, milnacipran, milnacipran + lithium effective as second-line therapy in depressive disorder patient suggest milnacipran + lithium likely effective if first-line therapy ineffective)

REFERENCE COUNT: 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 187 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2004:281647 HCAPLUS

DOCUMENT NUMBER: 141:343255

TITLE: Depression in primary care: effectiveness of venlafaxine extended-release in elderly patients. Observational study

AUTHOR(S): Cervera-Enguix, S.; Baca-Baldomero, E.; Garcia-Calvo, C.; Prieto-Lopez, R.

CORPORATE SOURCE: Faculty of Medicine, University Clinic, Psychiatry and Medical Psychology Department, University of Navarra, Pamplona, 31008, Spain

SOURCE: Archives of Gerontology and Geriatrics (2004), 38(3), 271-280

CODEN: AGGEDL; ISSN: 0167-4943

PUBLISHER: Elsevier.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Depression in the elderly is frequent but is often not recognized or treated as such. Few studies have assessed the effectiveness and tolerability of venlafaxine extended-release in patients over 60 yr in primary care. This study aims to demonstrate the effectiveness and safety of venlafaxine extended-release in depressive disorders in this kind of population. Observational, multicenter and prospective study in an outpatient population over 60 yr with depressive symptoms that needs pharmacol. treatment and with a min. score of 14 on the 17-items Hamilton rating scale for depression (HAM-D17). Effectiveness was assessed by HAM-D17. Physician's assessment of the patient's global status was also used and all the possible adverse effects were recorded. Venlafaxine

extended-release was administered for 6 mo at 75 mg per day dose, with the possibility of going up to 150 mg per day according to clin. criterion. Data of 1214 patients were obtained, with remission rates (HAM-D17 \leq 7) in 70.2% of the patients and response rates (50% decrease in HAM-D17) of 83.2%. Global assessment of the patient's status significantly improved in each visit. After 6 mo of treatment, 87.6% of the patients continued taking 75 mg per day of venlafaxine extended release. A total of 4.6% of the patients reported adverse events during the study. Venlafaxine extended-release is effective and safe for the treatment of depression in elderly patients managed by primary care physicians.

CC 1-11 (Pharmacology)

IT **Mental disorder**

(depression; venlafaxine extended-release showed good response, remission rates, tolerability and is effective and safe for treatment of **depression** in elderly patient with **depression**)

IT 93413-69-5, Venlafaxine

RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(venlafaxine extended-release showed good response, remission rates, tolerability and is effective and safe for treatment of **depression** in elderly patient with **depression**)

REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 188 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2004:1008648 HCAPLUS

DOCUMENT NUMBER: 142:233061

TITLE: A comparative study of milnacipran and paroxetine in outpatients with major depression

AUTHOR(S): Sechter, Daniel; Vandel, Pierre; Weiller, Emmanuel; Pezous, Nicole; Cabanac, Fabienne; Tournoux, Alain

CORPORATE SOURCE: Service de Psychiatrie de l'Adulte, Centre Hospitalier Universitaire St Jacques, Besancon, F-25030, Fr.

SOURCE: Journal of Affective Disorders (2004), 83(2-3), 233-236

CODEN: JADID7; ISSN: 0165-0327

PUBLISHER: Elsevier Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Milnacipran is a dual-action antidepressant which inhibits both serotonin and noradrenaline reuptake with no affinity for any neurotransmitter receptor studied. A 6-wk double-blind multicentre study compared milnacipran (100 mg/day) with paroxetine (20 mg/day) in 300 outpatients with major depression. Efficacy was evaluated using HAMD17, MADRS and CGI for severity of illness and global improvement. Data were analyzed on an intention to treat, last observation carried forward, basis. Milnacipran and paroxetine were both effective and well tolerated with no significant difference in their effects. After treatment discontinuation, milnacipran was associated with significantly less emergent symptoms. Responders, at endpoint, to milnacipran had significantly greater levels of psychomotor retardation at baseline than non-responders. The study did not include a placebo group so that it is impossible to determine absolute levels of efficacy.

Both milnacipran and paroxetine were effective and well tolerated by outpatients with major depression treated for 6 wk. After treatment discontinuation milnacipran was associated with less emergent symptoms.

Psychomotor retardation at baseline may be a predictive factor of a favorable response to milnacipran.

CC 1-11 (Pharmacology)

IT **Mental disorder**

(major **depression**; milnacipran, paroxetine were equally effective and well tolerated in outpatient with major **depression** while milnacipran was associated with less emergent symptoms after treatment discontinuation)

IT 61869-08-7, Paroxetine 92623-85-3, Milnacipran

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(milnacipran, paroxetine were equally effective and well tolerated in outpatient with major **depression** while milnacipran was associated with less emergent symptoms after treatment discontinuation)

REFERENCE COUNT: 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 189 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2004:211759 HCAPLUS

DOCUMENT NUMBER: 141:307342

TITLE: Remission in major depression with two antidepressant mechanisms: results from a naturalistic study

AUTHOR(S): Montes, Jose Manuel; Ferrando, Laura; Saiz-Ruiz, Jeronimo

CORPORATE SOURCE: Hospital Universitario Principe de Asturias, Universidad de Alcala, Madrid, Spain

SOURCE: Journal of Affective Disorders (2004), 79(1-3), 229-234

CODEN: JADID7; ISSN: 0165-0327

PUBLISHER: Elsevier Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Background: Since remission should be the goal of the treatment of depression, the aims of this study were to evaluate the rate of remission obtained with SSRIs in routine clin. practice and to assess alternative treatments with a combined mechanism of action. Methods: The study involved a prospective naturalistic 6-mo follow-up of 44 consecutive unipolar depressed (DSM-IV) outpatients. After 6 wk of treatment with a SSRI, patients were classified as remitted (HAM-D-17 score ≤ 7), partial responders ($\geq 50\%$ reduction in HAM-D-17 score but still higher than 7) and non-responders. In case of non-response, an antidepressant with noradrenergic action (NaA) was added to the ongoing SSRI treatment or were switched to venlafaxine in monotherapy when NaA was contraindicated. Results: At 6 wk, eight patients (18.1%) achieved full remission, nine patients (20.5%) were partial responders and 27 (61.4%) non responders. At the end of follow-up 31.8% (n=14) of the initial sample remained remitted with SSRIs, whereas 96.2% (26/27) of previous non-responders experienced remission with the alternative treatment. Non-responders to SSRIs in monotherapy were significantly more likely to show melancholic features and to have higher HAM-D-17 scores and lower GAF scores than remitted patients with SSRIs. Limitations: the observational and naturalistic design of the study dets. inherent limitations. Conclusions: this study showed a low remission rate with SSRIs in the long-term treatment of more severe and melancholic depression, and the benefit of using treatments with a combined mechanism of action.

CC 1-11 (Pharmacology)

IT **Mental disorder**

(major **depression**; long-term SSRIs treatment was associated with low remission rate in more severe and melancholic **depression**)

and combining SSRI with NaA showed benefits in patient with MD)
IT 303-49-1, Clomipramine 93413-69-5, Venlafaxine
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combination of SSRI and NaA with clomipramine showed beneficial effect in more severe and melancholic **depression** patient who showed low rate of remission with long-term SSRI monotherapy)
REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 190 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:662276 HCAPLUS
DOCUMENT NUMBER: 141:254324
TITLE: A double-blind; randomized, 26-week study comparing the cognitive and psychomotor effects and efficacy of 75 mg (37.5 mg b.i.d.) venlafaxine and 75 mg (25 mg mane, 50 mg nocte) dothiepin in elderly patients with moderate major depression being treated in general practice
AUTHOR(S): Trick, Leanne; Stanley, Neil; Rigney, Una; Hindmarch, Ian
CORPORATE SOURCE: HPRU Medical Research Centre, University of Surrey, Guildford, Surrey, UK
SOURCE: Journal of Psychopharmacology (London, United Kingdom) (2004), 18(2), 205-214
CODEN: JOPSEQ; ISSN: 0269-8811
PUBLISHER: Sage Publications Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB To investigate the efficacy and cognitive and psychomotor effects of venlafaxine and dothiepin in elderly patients with moderate major depression. A prospective, randomized, double-blind, parallel-group, active comparator controlled study was conducted. Eighty-eight patients (aged ≥ 60 yr) were enrolled. Each patient received either venlafaxine (immediate release formulation) 37.5 mg twice per day or dothiepin 25 mg mane followed by 50 mg nocte for 26 wk. Efficacy was assessed with the Montgomery-Asberg Depression Rating Scale and the Hamilton Depression Rating Scale. A psychometric test battery to assess cognitive function, activities of daily living and sleep consisted of Critical Flicker Fusion (CFF), Short-term Memory - Kim's Game, Cognitive Failures Questionnaire, Milford Epworth Sleepiness Scale, Leeds Sleep Evaluation Questionnaire, and an Accident Scoring Questionnaire. Quality of Life Questionnaires (Short Form 36 and Quality of Life in Depression Scale) were also administered. Venlafaxine significantly ($p < 0.05$) raised CFF scores compared to baseline but had no effect on any other measure. Dothiepin significantly ($p < 0.05$) lowered CFF threshold, and increased ratings of both sedation and difficulty in waking. The results showed that venlafaxine at doses of 37.5 mg b.i.d. in elderly depressed patients is free from disruptive effects on cognitive function and psychomotor performance.

CC 1-11 (Pharmacology)

IT **Mental disorder**

(major **depression**; cognitive and psychomotor effects and efficacy of venlafaxine and dothiepin in elderly patients with moderate major **depression**)

IT 113-53-1, Dothiepin 93413-69-5, Venlafaxine
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(cognitive and psychomotor effects and efficacy of venlafaxine and dothiepin in elderly patients with moderate major **depression**)

REFERENCE COUNT: 57 THERE ARE 57 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 191 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN
 ACCESSION NUMBER: 2004:662275 HCAPLUS
 DOCUMENT NUMBER: 141:254323
 TITLE: Tolerability of high-dose venlafaxine in depressed patients
 AUTHOR(S): Harrison, C. Louise; Ferrier, Nicol; Young, Allan H.
 CORPORATE SOURCE: School of Neurology, Neurobiology and Psychiatry, Psychiatry, Royal Victoria Infirmary, Newcastle upon Tyne, UK
 SOURCE: Journal of Psychopharmacology (London, United Kingdom) (2004), 18(2), 200-204
 CODEN: JOPSEQ; ISSN: 0269-8811
 PUBLISHER: Sage Publications Ltd.
 DOCUMENT TYPE: Journal
 LANGUAGE: English

AB High doses of antidepressants are often used for treatment-resistant depression. Venlafaxine, a dual serotonin and noradrenaline reuptake inhibitor, has been shown to have a tolerable side-effect profile in previous studies using doses of up to 375 mg/day. We investigated the tolerability of higher than currently recommended doses of venlafaxine using the UKU side-effect rating scale. Seventy outpatients fulfilling DSM-IV criteria for major depressive disorder were recruited into two demog. matched groups according to their daily dosage of venlafaxine: high dose n = 35 (≥ 375 mg/day, range 375-600 mg, average 437 mg/day) or standard dose n = 35 (< 375 mg/day, range 75-300 mg, average 195 mg/day).

Clin. characteristics were noted and the UKU side-effect rating scale was administered to a subsample of patients. The most frequently reported complaints in both groups were increased fatigue (48%), concentration difficulties (48%), sleepiness/sedation (37%), failing memory (44.4%) and weight gain (29.6%). Apart from weight gain, the complaints were experienced significantly more severely by the high-dose group. Six patients discontinued venlafaxine due to intolerable side-effects but only two of these patients were on a high dose. There was a tendency for mildly raised blood pressure in 10% of patients on an average dose of 342 mg/day. However, no difference between the two groups was found. This preliminary open study demonstrates that venlafaxine is tolerated at higher than British National Formulary recommended doses (i.e. up to 600 mg daily). However, increased frequency and severity of reported side-effects in the high-dose group are not associated with increased rates of discontinuation.

CC 1-11 (Pharmacology)

IT **Mental disorder**
 (major **depression**; tolerability of high-dose venlafaxine in depressed patients)

IT **93413-69-5, Venlafaxine**
 RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study);
 USES (Uses)
 (tolerability of high-dose venlafaxine in **depressed** patients)

REFERENCE COUNT: 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 192 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN
 ACCESSION NUMBER: 2004:649157 HCAPLUS

DOCUMENT NUMBER: 142:69019
 TITLE: Should Major Depression with High Normal'
 Thyroid-Stimulating Hormone Be Treated Preferentially
 with Tricyclics?
 AUTHOR(S): Corruble, Emmanuelle; Berlin, Ivan; Lemoine,
 Antoinette; Hardy, Patrick
 CORPORATE SOURCE: Psychiatry Department, Bicetre Hospital, Assistance
 Publique-Hopitaux de Paris, PSIGIM, Paris XI
 University, Paris, Fr.
 SOURCE: Neuropsychobiology (2004), 50(2), 144-146
 CODEN: NPBYAL; ISSN: 0302-282X
 PUBLISHER: S. Karger AG
 DOCUMENT TYPE: Journal
 LANGUAGE: English

AB In a prospective and naturalistic setting, two samples representing 209
 depressed in patients were assessed for thyroid functioning at admission
 before antidepressant treatment, and for depression before and after 1 mo
 of antidepressant treatment. The authors hypothesized that serum TSH
 elevation \geq upper 25th percentile of the normal reference range is
 associated with poorer response to antidepressant therapy and differences
 between tricyclic antidepressants (TCA) and other antidepressants.
 Screening for mild thyroid failure defined as serum TSH concns.
 \geq upper 25th percentile of the normal range may provide clues to the
 clinician. Such patients have a more severe form of depression and a
 slower or impaired response to antidepressant therapy. It is also
 possible that they would benefit preferentially from TCA rather than other
 antidepressants.

CC 1-11 (Pharmacology)
 Section cross-reference(s): 2

IT **Mental disorder**
 (major **depression**; depressed patient with high normal TSH
 level have severe form of **depression** and impaired response to
 antidepressant therapy with SSRI, SNRI like venlafaxine, milnacipran
 but may preferentially benefit from tricyclic antidepressants)

IT 92623-85-3, Milnacipran
 RL: PAC (Pharmacological activity); THU (Therapeutic
 use); BIOL (Biological study); USES (Uses)
 (depressed patient with high normal TSH level have severe
 form of **depression** and impaired response to antidepressant
 therapy with SNRI like milnacipran but may preferentially benefit from
 tricyclic antidepressants)

IT 93413-69-5, Venlafaxine
 RL: PAC (Pharmacological activity); THU (Therapeutic
 use); BIOL (Biological study); USES (Uses)
 (depressed patient with high normal TSH level have severe
 form of **depression** and impaired response to antidepressant
 therapy with SNRI like venlafaxine but may preferentially benefit from
 tricyclic antidepressants)

REFERENCE COUNT: 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS
 RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 193 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN
 ACCESSION NUMBER: 2004:719700 HCAPLUS
 DOCUMENT NUMBER: 142:85595
 TITLE: Metabolism of the newest antidepressants: comparisons
 with related predecessors
 AUTHOR(S): Caccia, Silvio
 CORPORATE SOURCE: Istituto di Ricerche Farmacologiche "Mario
 Negri", Milan, 20157, Italy

SOURCE: IDrugs (2004), 7(2), 143-150
CODEN: IDRUFN; ISSN: 1369-7056
PUBLISHER: Thomson Scientific
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. The need for better acute and long-term treatment for depressive disorders has led to the development of new agents, including escitalopram, duloxetine (Boehringer Ingelheim Corp/Eli Lilly & Corp/Eli Lilly Japan KK/Shionogi & Co Ltd) and gepirone. These drugs undergo extensive biotransformation, with cytochrome P 450 (CYP) isoforms playing a major role. Escitalopram is biotransformed by CYP2C19, CYP3A4 and CYP2D6; partly extrapolating from studies of citalopram, polymorphism at CYP2C19 and drug interactions at CYP2D6 may be clin. significant. Duloxetine is metabolized by CYP2D6 and CYP1A2, with moderate potential for interactions at CYP2D6. The metabolism of gepirone involves CYP3A4 and to a lesser extent CYP2D6.
CC 1-0 (Pharmacology)
IT **Mental disorder**
(**depression**; pharmacokinetics and pharmacodynamics studies revealed new antidepressants escitalopram, duloxetine and gepirone undergo extensive biotransformation with cytochrome P 450 isoforms playing major role in depressed patient)
IT 116539-59-4, Duloxetine
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(new antidepressant duloxetine is metabolized by CYP2D6 and CYP1A2 with moderate potential for interactions at CYP2D6 in **depressed** patient)
REFERENCE COUNT: 66 THERE ARE 66 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 194 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:136317 HCAPLUS
DOCUMENT NUMBER: 141:306667
TITLE: How to treat bipolar II depression and bipolar II mixed depression?
AUTHOR(S): Benazzi, Franco
CORPORATE SOURCE: E. Hecker Outpatient Psychiatry Center, Ravenna, Italy
SOURCE: International Journal of Neuropsychopharmacology
(2004), 7(1), 105-106
CODEN: IJNUFB; ISSN: 1461-1457
PUBLISHER: Cambridge University Press
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review discusses various studies evaluating the treatment of bipolar II (BP II) depression and the mixture of BP II depression. In a study, fluoxetine and venlafaxine were shown to be effective in BP II depression and had low risk of switching. In the cases of mixed BP II depression, there are some clin. observations on the possible worsening of BP II depression by antidepressants. Due to cases, clinicians should be aware that BP II depression is often mixed, and that this mixture of some excitement symptoms with the inhibition of depression may be a difficult treatment challenge.
CC 1-0 (Pharmacology)
IT **Mental disorder**
(bipolar disorder; bipolar II **depression** and bipolar II mixed **depression** treatment)
IT **Mental disorder**
(**depression**; bipolar II **depression** and bipolar II

mixed depression treatment)
IT 54910-89-3, Fluoxetine 93413-69-5, Venlafaxine
RL: PAC (Pharmacological activity); THU (Therapeutic
use); BIOL (Biological study); USES (Uses)
(bipolar II depression and bipolar II mixed
depression treatment)
REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 195 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:242105 HCAPLUS
DOCUMENT NUMBER: 140:332348
TITLE: Effects of the novel antidepressant milnacipran in a
chronic mild stress model of depression
AUTHOR(S): Papp, Mariusz; Panconi, Emmanuel; Gruca, Piotr
CORPORATE SOURCE: Institute of Pharmacology, Polish Academy of Sciences,
Krakow, Pol.
SOURCE: Drug Development Research (2004), 61(2), 101-106
CODEN: DDREDK; ISSN: 0272-4391
PUBLISHER: Wiley-Liss, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The chronic mild stress (CMS) model of depression may serve as a suitable
research tool for studying the action of novel antidepressants (i.e., both
efficacy and onset of action). The CMS-induced sub-sensitivity to reward
is reversed by chronic treatment with antidepressant drugs. The effect of
the serotonin and norepinephrine reuptake inhibitor (SNRI), milnacipran,
was investigated on the CMS model in rats in comparison with imipramine.
The CMS model of depression consisted in subjecting rats to several mild
stressors for a prolonged period of time, which resulted in a decrease in
their responsiveness to rewarding stimuli. This deficit was monitored by
a decrease in the consumption of a 1% sucrose solution. Stressed and control
animals received daily for 5 wk injections of vehicle, imipramine (10
mg/kg) or milnacipran (3, 10, and 30 mg/kg). CMS caused a decrease in the
consumption of the 1% sucrose solution. The deficit in sucrose consumption in
stressed animals was reversed by imipramine and milnacipran. The effect
of milnacipran was gradual, dose-dependent, and was maintained for one
week after stopping drug treatment. Neither imipramine nor milnacipran
modified the behavior of control animals. Milnacipran is active in the
CMS model of depression as expected from its clin. demonstrated
antidepressant effect.

CC 1-11 (Pharmacology)

IT Mental disorder
(depression; effects of antidepressant milnacipran in chronic
mild stress model of depression)

IT 92623-85-3, Milnacipran
RL: PAC (Pharmacological activity); THU (Therapeutic
use); BIOL (Biological study); USES (Uses)
(effects of antidepressant milnacipran in chronic mild stress model of
depression)

REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 196 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:464028 HCAPLUS
DOCUMENT NUMBER: 142:32809
TITLE: Reboxetine adjunct for partial or nonresponders to
antidepressant treatment
AUTHOR(S): Rubio, Gabriel; San, Luis; Lopez-Munoz, Francisco;

Alamo, Cecilio
 CORPORATE SOURCE: Psychiatry Service, "La Paz" University Hospital,
 Madrid, Spain
 SOURCE: Journal of Affective Disorders (2004), 81(1), 67-72
 CODEN: JADID7; ISSN: 0165-0327
 PUBLISHER: Elsevier Ltd.
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 AB Background: To investigate the usefulness of the combination therapy with
 two antidepressants from different pharmacol. families in
 treatment-resistant depressive patients. Methods: In this prospective 6
 wk open-label study, we assessed the effectiveness of the addition of
 reboxetine to 61 depressive patients that had previously not responded, or
 had done so only in a partial way, to conventional treatment, in
 monotherapy, with selective serotonin reuptake inhibitors (SSRIs),
 venlafaxine or mirtazapine. Data were analyzed on an intent-to-treat
 basis, using the last-observation-carried-forward (LOCF) method. Results:
 Mean decrease on the 21-item Hamilton Depression Rating Scale (HDRS) score
 was 48.9% and on the Clin. Global Impressions Scale (CGI), 38.9%. At the
 end of the treatment, 62.3% of the patients were evaluated as improvement
 (CGI<4), 54.1% as responders (HDRS≤50%) and 45.9% in remission
 (HDRS≤10). No serious side effects were observed during combination
 therapy, being more frequent increased sweating (8.2%) and dry mouth
 (6.6%). Conclusions: These findings suggest that the strategy of
 combination with reboxetine may be an effective and well-tolerated tool in
 treatment-resistant patients who have failed to adequately respond to
 monotherapy with SSRIs, venlafaxine or mirtazapine.
 CC 1-11 (Pharmacology)
 IT **Mental disorder**
 (depression; selective serotonin reuptake inhibitors in
 combination with reboxetine may be effective and well-tolerated tool in
 treatment-resistant **depression** patient who failed to respond
 to monotherapy with SSRIs, venlafaxine or mirtazapine)
 IT **93413-69-5, Venlafaxine**
 RL: ADV (Adverse effect, including toxicity); **PAC (Pharmacological**
activity); **THU (Therapeutic use)**; BIOL (Biological study);
 USES (Uses)
 (venlafaxine in combination with reboxetine may be effective and
 well-tolerated tool and showed adverse effects like increased sweating,
 dry mouth, tremor in treatment-resistant **depression** patient
 who failed to respond to monotherapy)
 REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS
 RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 197 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN
 ACCESSION NUMBER: 2004:462948 HCAPLUS
 DOCUMENT NUMBER: 142:32803
 TITLE: A Randomised Study Comparing Escitalopram with
 Venlafaxine XR in Primary Care Patients with Major
 Depressive Disorder
 AUTHOR(S): Montgomery, S. A.; Huusom, A. K. T.; Bothmer, J.
 CORPORATE SOURCE: Imperial College School of Medicine, London, W13 8WH,
 UK
 SOURCE: Neuropsychobiology (2004), 50(1), 57-64
 CODEN: NPBIAL; ISSN: 0302-282X
 PUBLISHER: S. Karger AG
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 AB This 8-wk, randomized, double-blind study compared the efficacy and

tolerability of escitalopram to that of venlafaxine XR in primary care patients with major depressive disorder. The efficacy of escitalopram (10- 20 mg; n = 148) was similar to venlafaxine XR (75- 150 mg; n = 145), based on mean change from baseline to week 8 in Montgomery and Åsberg Depression Rating Scale total score. In ad hoc analyses, escitalopram-treated patients achieved sustained remission significantly faster than did venlafaxine-treated patients. More venlafaxine-treated patients had nausea, constipation, and increased sweating ($p < 0.05$). When treatment was completed after 8 wk, significantly more venlafaxine-treated patients had discontinuation symptoms ($p < 0.01$). Thus escitalopram treatment was similar to venlafaxine treatment with respect to efficacy and was better tolerated by patients in primary care.

CC 1-11 (Pharmacology)

IT **Mental disorder**

(major **depression**; escitalopram treatment was similar to venlafaxine XR with resp. to efficacy and was better tolerated in primary care patient with major depressive disorder)

IT 93413-69-5, Venlafaxine 128196-01-0, Escitalopram

RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(escitalopram treatment was similar to venlafaxine XR with resp. to efficacy and was better tolerated in primary care patient with major depressive disorder)

REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 198 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2004:136305 HCAPLUS

DOCUMENT NUMBER: 141:236231

TITLE: Augmentation of milnacipran by risperidone in treatment for major depression

AUTHOR(S): Tani, Kunihiro; Takei, Nori; Kawai, Masayoshi; Suzuki, Katsuaki; Sekine, Yoshimoto; Toyoda, Takao; Minabe, Yoshio; Mori, Norio

CORPORATE SOURCE: Department of Psychiatry and Neurology, Hamamatsu University School of Medicine, Hamamatsu, Shizuoka, 431-3192, Japan

SOURCE: International Journal of Neuropsychopharmacology (2004), 7(1), 55-58

CODEN: IJNUFB; ISSN: 1461-1457

PUBLISHER: Cambridge University Press

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Milnacipran, one of the serotonin noradrenaline reuptake inhibitors (SNRIs) to which venlafaxine and duloxetine belong, is a new antidepressant that has recently become available in many countries. Despite the advances in pharmacotherapy, almost one third of patients with depressive illness respond inadequately to monotherapy with such an antidepressant. We herein describe five patients with major depression who responded partially, but not fully, to milnacipran alone and remarkably improved with an adjunct of risperidone. In addition, milnacipran plus risperidone was found to be a useful augmentation for treatment-refractory depression in 3 of the 5 patients. The min. dose of risperidone, 0.5 or 1 mg/d, was efficacious. The time of response after addition of risperidone was within 4 d. Our experience suggests that an augmentation therapy of milnacipran plus risperidone is useful for treating patients with depression who only partially respond to various types of antidepressants and for treatment-refractory depression.

CC 1-11 (Pharmacology)

IT **Mental disorder**

(major **depression**; adjunctive therapy with risperidone significantly improved **depression** symptoms in major **depression** patient partially responded to milnacipran and risperidone plus milnacipran found to be useful in treatment of refractory **depression**)

IT 92623-85-3, Milnacipran 106266-06-2, Risperidone

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(adjunctive therapy with risperidone significantly improved **depression** symptoms in major **depression** patient partially responded to milnacipran and risperidone plus milnacipran found to be useful in treatment of refractory **depression**)

REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 199 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2004:315145 HCAPLUS

DOCUMENT NUMBER: 141:218781

TITLE: An open-label clinical trial of milnacipran in fibromyalgia syndrome with co-morbid depressive symptoms

AUTHOR(S): Nagaoka, Shouhei; Ohno, Mikako; Sekiguchi, Akiko

CORPORATE SOURCE: Department of Rheumatology, Yokohama Minami Kyosai Hospital, Kanagawa, Japan

SOURCE: International Journal of Psychiatry in Clinical Practice (2004), 8(1), 47-51

CODEN: IJPCFZ; ISSN: 1365-1501

PUBLISHER: Taylor & Francis

DOCUMENT TYPE: Journal

LANGUAGE: English

AB OBJECTIVE: To evaluate the efficacy of the serotonin and noradrenaline reuptake inhibiting antidepressant, milnacipran, in patients with fibromyalgia syndrome and comorbid depression. METHODS: Twenty patients with fibromyalgia syndrome and comorbid depressive symptoms were treated with the serotonin and noradrenaline reuptake inhibitor, milnacipran, in an open label study. The initial dose of milnacipran was 30 mg/day which could be increased as needed up to 100 mg/day. Patients were evaluated at baseline and after 4, 8 and 12 wk of treatment. Pain level and global symptomatol. were determined using visual analog scales. Pain was also accessed by use of the face scale, while the severity of depression was determined using the Zung self-rating depression scale. RESULTS: Two patients withdrew because of persistent nausea. Pain and general symptomatol. were significantly improved at the end of the study, with five patients having a reduction in pain of greater than 50%. Posthoc anal. showed that the 11 patients who were no longer depressed at the end of the study had the greatest improvement in pain and overall FMS symptomatol. CONCLUSION: The data suggest that milnacipran may be effective in the treatment of FMS, especially when associated with depression.

CC 1-11 (Pharmacology)

IT **Mental disorder**

(**depression**; milnacipran in fibromyalgia syndrome with co-morbid depressive symptoms)

IT 101152-94-7, Milnacipran hydrochloride

RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(Ixel, Toledomin, Dalcipran; milnacipran in fibromyalgia syndrome with

co-morbid **depressive** symptoms)

REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 200 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2004:364164 HCAPLUS

DOCUMENT NUMBER: 141:324988

TITLE: Newer antidepressants: review of efficacy and safety
of escitalopram and duloxetine

AUTHOR(S): Hirschfeld, Robert M. A.; Vornik, Lana A.

CORPORATE SOURCE: Department of Psychiatry and Behavioral Sciences,
University of Texas-Medical Branch, Galveston, USA

SOURCE: Journal of Clinical Psychiatry (2004), 65(Suppl. 4),
46-52

CODEN: JCLPDE; ISSN: 0160-6689

PUBLISHER: Physicians Postgraduate Press, Inc.

DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

AB A review. Background: Two antidepressants with different mechanisms of
action, escitalopram and duloxetine, have recently been developed for the
treatment of major depressive disorder. This article reviews the
available controlled data on these agents with regard to efficacy, safety,
and tolerability. Method: We identified four 8-wk, double-blind,
placebo-controlled studies of escitalopram in the acute treatment of major
depression. Three of the studies involved an active comparator,
citalopram. We identified 6 placebo-controlled studies of duloxetine in
major depressive disorder. Two of the studies included fluoxetine as an
active comparator, and 2 included paroxetine as an active comparator.
Results: A review of the data from the controlled studies supports the
efficacy of both escitalopram and duloxetine in the treatment of patients
with major depression. Three of the 4 escitalopram studies were pos., and
1 was a failed study. Four of the 6 duloxetine studies were pos. Both
escitalopram and duloxetine performed better than at least 1 selective
serotonin reuptake inhibitor comparator. The safety and tolerability
profiles of both drugs are quite benign. The reported incidence of
treatment-emergent adverse events was somewhat lower with escitalopram
than with duloxetine, with the possible exception of sexual dysfunction.
Discontinuations due to adverse events were lower for escitalopram than
for duloxetine, although rates were comparable with higher doses of
escitalopram (20 mg/day). Conclusion: Both escitalopram and duloxetine
are useful in the treatment of major depressive disorder.

CC 1-0 (Pharmacology)

IT **Mental disorder**

(major **depression**; antidepressants escitalopram, duloxetine
was safe, tolerable and effective in treatment of major depressive
disorder and escitalopram had less adverse events than duloxetine in
human)

IT 59729-33-8, Citalopram 116539-59-4, Duloxetine 128196-01-0,
Escitalopram

RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological
activity); THU (Therapeutic use); BIOL (Biological study);
USES (Uses)

(antidepressants escitalopram, duloxetine was safe, tolerable and
effective in treatment of major **depressive** disorder and
escitalopram had less adverse events than duloxetine in human)

REFERENCE COUNT: 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 201 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2004:364162 HCAPLUS
DOCUMENT NUMBER: 141:324987
TITLE: Selective versus multi-transmitter antidepressants:
are two mechanisms better than one?
AUTHOR(S): Burke, William J.
CORPORATE SOURCE: Department of Psychiatry, University of Nebraska,
Omaha, USA
SOURCE: Journal of Clinical Psychiatry (2004), 65(Suppl. 4),
37-45
CODEN: JCLPDE; ISSN: 0160-6689
PUBLISHER: Physicians Postgraduate Press, Inc.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. The issue of selectivity vs. efficacy has now reappeared as
newer agents have emerged that are less selective than the selective
serotonin reuptake inhibitors (SSRIs) but more selective than the
tricyclic antidepressants (TCAs). This article provides a critical
examination of
the clin. literature concerning what evidence-there is for differential
efficacy. Two broad areas will be discussed: (1) comparisons of SSRIs to
TCAs and (2) comparisons of the SSRIs to a somewhat more selective compound
(by comparison to the TCAs), venlafaxine. This review should caution one
in accepting claims of superiority of any agent based on purported
mechanism of action.
CC 1-0 (Pharmacology)
IT **Mental disorder**
(**depression**; SSRI was compared with TCA and more selective
compds. like venlafaxine revealed that drugs that impact both
serotonergic and adrenergic receptors are more efficacious but are
associated with adverse events in patient with **depression**)
IT 93413-69-5, Venlafaxine
RL: PAC (**Pharmacological activity**); THU (**Therapeutic**
use); BIOL (Biological study); USES (Uses)
(SSRI was compared with TCA and more selective compds. like venlafaxine
revealed that drugs that impact both serotonergic and adrenergic
receptors are more efficacious but are associated with adverse events in
patient with **depression**)
REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 202 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:120490 HCAPLUS
DOCUMENT NUMBER: 140:175028
TITLE: Acute and continuation treatment adequacy with
venlafaxine extended release compared with fluoxetine
AUTHOR(S): Yu-Isenberg, Kristina S.; Fontes, Christina L.; Wan,
George J.; Geissler, Erika C.; Harada, Ann S. M.
CORPORATE SOURCE: Pharmacoeconomics and Health Outcomes Research
Department, Prescription Solution, Costa Mesa, CA, USA
SOURCE: Pharmacotherapy (2004), 24(1), 33-40
CODEN: PHPYDQ; ISSN: 0277-0008
PUBLISHER: Pharmacotherapy Publications
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Study Objective: To compare treatment adequacy in the management of
depression during the acute and continuation phases between patients newly
treated with venlafaxine extended release (XR) and those newly treated
with fluoxetine. Design: Retrospective observational anal. of pharmacy
claims data. Setting: Large California-based managed care organization.

Patients: A total of 11,298 patients newly prescribed venlafaxine XR or fluoxetine between Jan. 1, 2000, and Feb. 28, 2001, and continuously enrolled throughout the study, as well as a subset of 7430 patients who continued taking venlafaxine XR or fluoxetine during the follow-up period. Measurements and Main Results: The Health Plan Employer Data and Information Set definition was used for continuous antidepressant treatment during the acute and continuation phases. Treatment adequacy was determined for those deemed continuous. Patients receiving within $\pm 10\%$ of the target dose for each drug (venlafaxine XR 75 - 150 mg, fluoxetine 20 mg) were defined as receiving an adequate dose. Logistic regression was used to evaluate venlafaxine XR vs. fluoxetine on treatment adequacy, controlling for age, sex, physician specialty, and pharmacy benefit. The unadjusted adequacy rate for the venlafaxine XR-only group was 79% vs. 57% for the fluoxetine-only group for 84 continuous days ($p < 0.0001$) and 77% vs. 52%, resp., for 180 continuous days ($p < 0.0001$). The adjusted odds ratios of achieving treatment adequacy with venlafaxine XR only vs. that with fluoxetine only were 3.05 (95% confidence interval [CI] 2.65 - 3.52) for 84 continuous days and 3.57 (95% CI 3.00 - 4.24) for 180 continuous days. Conclusion: Patients newly prescribed venlafaxine XR were at least 3 times more likely to achieve treatment adequacy for 84 and 180 days compared with those newly prescribed fluoxetine. Treatment adequacy as a proxy for optimal treatment may be an important factor to consider when selecting an antidepressant drug.

CC 1-11 (Pharmacology)

Section cross-reference(s): 63

IT **Mental disorder**

(**depression**; venlafaxine extended release vs. fluoxetine for acute and continuation treatment adequacy in patients with **depression**)

IT 54910-89-3, Fluoxetine 93413-69-5, Venlafaxine

RL: **PAC (Pharmacological activity)**; **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)

(venlafaxine extended release vs. fluoxetine for acute and continuation treatment adequacy in patients with **depression**)

REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 203 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2004:975132 HCAPLUS

DOCUMENT NUMBER: 142:309632

TITLE: A double-blind placebo-controlled trial of milnacipran in the treatment of fibromyalgia

AUTHOR(S): Vitton, Olivier; Gendreau, Michael; Gendreau, Judy; Kranzler, Jay; Rao, Srinivas G.

CORPORATE SOURCE: Cypress Bioscience, San Diego, USA

SOURCE: Human Psychopharmacology (2004), 19(Suppl. 1), S27-S35
CODEN: HUPSEC; ISSN: 0885-6222

PUBLISHER: John Wiley & Sons Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Fibromyalgia syndrome is a systemic disorder of widespread pain which is thought to result from abnormal pain processing within the central nervous system. There are no currently approved treatments for this indication. Antidepressants appear, however, to be effective, especially those with an action on noradrenergic neurotransmission. The objective of the present study was to test the efficacy of the dual action noradrenaline and serotonin reuptake inhibitor antidepressant, milnacipran, in the treatment of fibromyalgia. The 125 patients, who were enrolled in a double-blind, placebo-controlled, flexible dose escalation trial, were randomized to

receive placebo or milnacipran for 4 wk of dose escalation (up to 200 mg/day), followed by 8 wk at a constant dose. The study evaluated the efficacy and safety of milnacipran for the treatment of **pain** and associated symptoms such as fatigue, **depressed** mood and sleep. 75% Of milnacipran-treated patients reported overall improvement, compared with 38% in the placebo group ($p < 0.01$). Furthermore, 37% of twice daily milnacipran-treated patients reported at least 50% reduction in pain intensity, compared with 14% of placebo-treated patients ($p < 0.05$). 84% Of all milnacipran patients escalated to the highest dose (200 mg/day) with no tolerability issues. Most adverse events were mild to moderate in intensity, and transient in duration. These results suggest that milnacipran may have the potential to relieve not only pain but several of the other symptoms associated with fibromyalgia.

CC 1-11 (Pharmacology)

ST **antidepressant** milnacipran **pain** fatigue
depression sleep fibromyalgia

IT **Nervous system agents**

(**noradrenaline reuptake inhibitors**;

milnacipran in treatment of patients with fibromyalgia)

REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 204 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2004:1032653 HCAPLUS

DOCUMENT NUMBER: 142:127389

TITLE: Pretreatment neurophysiological and clinical characteristics of placebo responders in treatment trials for major depression

AUTHOR(S): Leuchter, Andrew F.; Morgan, Melinda; Cook, Ian A.; Dunkin, Jennifer; Abrams, Michelle; Witte, Elise

CORPORATE SOURCE: UCLA NPI, Los Angeles, CA, 90024-1759, USA

SOURCE: Psychopharmacology (Berlin, Germany) (2004), 177(1-2), 15-22

CODEN: PSCHDL; ISSN: 0033-3158

PUBLISHER: Springer GmbH

DOCUMENT TYPE: Journal

LANGUAGE: English

AB High placebo response rates are a confound in treatment trials for major depressive disorder (MDD). A method for prospective identification of placebo responders could enhance the efficiency of clin. trials. The objective was to identify the neurophysiol., symptomatic, and cognitive characteristics of subjects who were likely to respond to placebo in clin. trials for MDD. Fifty-one subjects with MDD were treated in clin. trials with either fluoxetine (n=24) or venlafaxine (n=27) vs. placebo. All subjects underwent pretreatment assessment with quant. electroencephalog. (QEEG) power and cordance, as well as symptom ratings and neuropsychol. testing. After a 1-wk single-blind placebo lead-in, subjects were randomized to double-blind placebo controlled treatment with a medication or placebo. At the end of 8 wk, the blind was broken and treatment response assessed. Response was defined by a final Hamilton Depression Rating Scale score of ≤ 10 . Of the medication-treated and placebo-treated subjects, 52 (13/25) and 38 (10/26) responded. Placebo responders had lower pretreatment frontocentral cordance in the theta frequency band than all other subjects ($P < 0.006$) and medication responders in particular ($P < 0.004$). Placebo responders also had faster cognitive processing time, as assessed by neuropsychol. testing, and lower reporting of late insomnia ($P < 0.03$). Exploratory examination of a multiple variable model for predicting placebo response was conducted using logistic regression, in which these three pretreatment measures accurately

identified 97.6 of eventual placebo responders. These findings suggest that combined clin., neurophysiol., and cognitive assessments of prospective subjects for clin. trials may be useful for identifying MDD subjects who are likely to show robust response to placebo. Prospective validation of these results in a larger, independent sample of subjects is necessary to establish the reliability and usefulness of this method for prospective identification of placebo responders.

CC 1-11 (Pharmacology)

IT **Mental disorder**

(major **depression**; pretreatment neurophysiol. and clin. characteristics of placebo responders in treatment trials for major **depression**)

IT 54910-89-3, Fluoxetine 93413-69-5, Venlafaxine

RL: **PAC (Pharmacological activity)**; BIOL (Biological study)

(pretreatment neurophysiol. and clin. characteristics of placebo responders in treatment trials for major **depression**)

REFERENCE COUNT: 46 THERE ARE 46 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 205 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2004:13452 HCAPLUS

DOCUMENT NUMBER: 141:184940

TITLE: Associations Between Baseline Plasma MHPG (3-methoxy-4-hydroxyphenylglycol) Levels and Clinical Responses With Respect to Milnacipran Versus Paroxetine Treatment

AUTHOR(S): Shinkai, Koji; Yoshimura, Reiji; Ueda, Nobuhisa; Okamoto, Kana; Nakamura, Jun

CORPORATE SOURCE: Department of Psychiatry, University of Occupational and Environmental Health, 1-1 Iseigaoka Yahatanishi-ku, fukuoka, 807-8555, Japan

SOURCE: Journal of Clinical Psychopharmacology (2004), 24(1), 11-17

CODEN: JCPYDR; ISSN: 0271-0749

PUBLISHER: Lippincott Williams & Wilkins

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The purpose of this study was to investigate the effects of milnacipran and paroxetine on plasma levels of catecholamine metabolites, and we attempted to elucidate the differences between the mechanisms of these drugs in catecholaminergic neurons. In depressed patients, we investigated the relationships among pretreatment levels of catecholamine metabolites, the changes in plasma catecholamine metabolite levels before and after administration of milnacipran or paroxetine, and clin. response to these drugs. Responders to milnacipran showed lower pretreatment levels of plasma 3-methoxy-4-hydroxyphenylglycol (pMHPG) than did nonresponders to milnacipran; there was also a pos. correlation between changes in pMHPG levels and percent improvement of the score on the 17-item Hamilton Rating Scale for Depression (HRSD). On the other hand, responders to paroxetine showed higher pretreatment levels of pMHPG than did nonresponders to paroxetine, and a neg. correlation was observed between changes in pMHPG levels and percent improvement of the HRSD score. However, a significant difference was not observed in the pretreatment plasma level of homovanillic acid between responders and nonresponders to treatment with milnacipran or paroxetine. These results suggest that there is an association between baseline pMHPG levels and clin. responses with respect to milnacipran vs. paroxetine treatment.

CC 1-11 (Pharmacology)

IT **Mental disorder**

(**depression**; milnacipran shows better response in **depression** patient with lower pretreatment levels of pMHPG and paroxetine shows better response in patient with higher pretreatment pMHPG level)

IT 92623-85-3, Milnacipran

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(milnacipran shows better response in **depression** patient with lower pretreatment levels of pMHPG)

REFERENCE COUNT: 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 206 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2004:165478 HCAPLUS

DOCUMENT NUMBER: 140:192017

TITLE: The treatment of depression with different formulations of venlafaxine: a comparative analysis

AUTHOR(S): Olver, James S.; Burrows, Graham D.; Norman, Trevor R.

CORPORATE SOURCE: Department of Psychiatry, Austin Hospital, University of Melbourne, Heidelberg, Victoria, Australia

SOURCE: Human Psychopharmacology (2004), 19(1), 9-16

CODEN: HUPSEC; ISSN: 0885-6222

PUBLISHER: John Wiley & Sons Ltd.

DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

AB A review. Venlafaxine is the first of a group of antidepressants that show dual reuptake inhibition of serotonin and noradrenaline (SNRIs). Originally marketed in an immediate release (IR) formulation a microencapsulated, extended release (XR) formulation is now available. Significant differences exist between these two formulations with respect to pharmacokinetic parameters which have an impact on clin. use. The XR has lower maximum plasma concns. (Cmax) and achieves these at a later time (higher Tmax). The longer apparent elimination half-life of the drug after single XR doses suggests that it is suitable for once daily dosing compared with the twice daily dosing regimen required by the IR formulation. With respect to antidepressant efficacy the XR formulation is equivalent to other marketed antidepressants and to the IR formulation. Consistent with its pharmacokinetic properties the use of the XR formulation is associated with less nausea and dizziness at the initiation of therapy. While in clin. usage XR might be expected to increase compliance with medication and to reduce discontinuation syndromes there are few comparative studies for which this has been evaluated. The XR formulation of venlafaxine is no worse than the IR form with respect to tolerability and offers some benefits to patients in terms of ease of use. On the other hand there does not appear to be any increase in the efficacy of the active agent.

CC 1-0 (Pharmacology)

IT **Mental disorder**

(**depression**; treatment of **depression** with different formulations of venlafaxine)

IT 93413-69-5, Venlafaxine

RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(treatment of **depression** with different formulations of venlafaxine)

REFERENCE COUNT: 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 207 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2005:64252 HCAPLUS

DOCUMENT NUMBER: 142:107261

TITLE: Duloxetine for the long-term treatment of major depressive disorder in patients aged 65 and older: An open-label study

AUTHOR(S): Wohlrreich, Madelaine M.; Mallinckrodt, Craig H.; Watkin, John G.; Hay, Donald P.

CORPORATE SOURCE: Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, IN, 46285, USA

SOURCE: BMC Geriatrics (2004), 4, No pp. given

CODEN: BGMECR; ISSN: 1471-2318

URL: <http://www.biomedcentral.com/content/pdf/1471-2318-4-11.pdf>

PUBLISHER: BioMed Central Ltd.

DOCUMENT TYPE: Journal; (online computer file)

LANGUAGE: English

AB Late-life depression is a common, chronic and recurring disorder for which guidelines recommend long-term therapy. The safety and efficacy of duloxetine for the treatment of major depressive disorder (MDD) were evaluated using data from elderly patients (age ≥ 65 years; $n=101$) who participated in a large, multinational, open-label study. Patients meeting DSM-IV criteria for MDD received duloxetine 80 mg/d (40 mg twice daily (BID)) to 120 mg/d (60 mg BID) for up to 52 wk. Efficacy measures included the Clin. Global Impression of Severity (CGI-S) scale, the 17-item Hamilton Rating Scale for Depression (HAM-D17), the Beck Depression Inventory-II (BDI-II), the Patient Global Impression of Improvement (PGI-I) scale, and the Sheehan Disability Scale (SDS). Safety and tolerability were evaluated using discontinuation rates, spontaneously reported adverse events, and changes in vital signs, ECG, and laboratory analytes. Mean changes in HAM-D17 total score at Weeks 6, 28, and 52 were -13.0, -17.4 and -17.5 (all p -values $<.001$). Significant improvement ($p<.001$) in both clinician- (CGI-S) and patient-rated (PGI-I) measures of improvement were observed at Week 1 and sustained throughout the study. Observed case response rates at Weeks 6, 28, and 52 were 62.9%, 84.9%, and 89.4%, resp., while the corresponding rates of remission were 41.4%, 69.8%, and 72.3%. Adverse events led to discontinuation in 27 (26.7%) patients. Treatment-emergent adverse events reported by $>10\%$ of patients included dizziness, nausea, constipation, somnolence, insomnia, dry mouth, and diarrhea. Most events occurred early in the study. Mean changes at endpoint in blood pressure and body weight were less than 2.0 mm Hg, and -0.1 kg, resp. In this open-label study, duloxetine was effective, safe, and well tolerated in the long-term treatment of MDD in patients aged 65 and older.

CC 1-11 (Pharmacology)

IT **Mental disorder**(major **depression**; duloxetine for treatment of major depressive disorder in patients aged 65 and older)IT **116539-59-4, Duloxetine**

RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study);

USES (Uses)

(duloxetine for treatment of major **depressive** disorder in patients aged 65 and older)

REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 208 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2004:2708 HCAPLUS

DOCUMENT NUMBER: 140:53450
 TITLE: Serotonin reuptake inhibitor combination with a GABAB receptor antagonist for the treatment of depression and other disorders
 INVENTOR(S): Mork, Arne; Cremers, Thomas Ivo Franciscus Hubert; Willigers, Sandra
 PATENT ASSIGNEE(S): H. Lundbeck A/S, Den.
 SOURCE: PCT Int. Appl., 42 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004000326	A1	20031231	WO 2003-DK412	20030619
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2490638	AA	20031231	CA 2003-2490638	20030619
BR 2003011503	A	20050222	BR 2003-11503	20030619
EP 1545552	A1	20050629	EP 2003-729907	20030619
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
JP 2005533069	T2	20051104	JP 2004-514582	20030619
PRIORITY APPLN. INFO.:				
			DK 2002-943	A 20020620
			US 2002-390851P	P 20020620
			WO 2003-DK412	W 20030619

AB The invention relates to the use of a compound, which is a serotonin reuptake inhibitor, and another compound, which is a GABAB receptor antagonist, inverse agonist or partial agonist for the preparation of a pharmaceutical composition for the treatment of depression, anxiety disorders and other affective disorders, such as generalized anxiety disorder, panic anxiety, obsessive compulsive disorder, acute stress disorder, post traumatic stress disorder and social anxiety disorder, eating disorders such as bulimia, anorexia and obesity, phobias, dysthymia, premenstrual syndrome, cognitive disorders, impulse control disorders, attention deficit hyperactivity disorder, drug abuse or any other disorder responsive to serotonin reuptake inhibitors.

IC ICM A61K031-662

ICS A61K031-343

CC 1-11 (Pharmacology)

IT **Mental disorder**

(affective; serotonin reuptake inhibitor combination with a GABAB receptor modulator for treatment of **depression** and other disorders)

IT **Mental disorder**

(attention deficit hyperactivity disorder; serotonin reuptake inhibitor combination with a GABAB receptor modulator for treatment of **depression** and other disorders)

IT **Mental disorder**

(cognitive; serotonin reuptake inhibitor combination with a GABAB receptor modulator for treatment of **depression** and other disorders)

IT **Mental disorder**

(**depression**; serotonin reuptake inhibitor combination with a GABAB receptor modulator for treatment of **depression** and other disorders)

IT **Mental disorder**

(impulse control disorder; serotonin reuptake inhibitor combination with a GABAB receptor modulator for treatment of **depression** and other disorders)

IT **Mental disorder**

(neurotic **depression**; serotonin reuptake inhibitor combination with a GABAB receptor modulator for treatment of **depression** and other disorders)

IT **Mental disorder**

(obsession-compulsion; serotonin reuptake inhibitor combination with a GABAB receptor modulator for treatment of **depression** and other disorders)

IT **Mental disorder**

(phobia; serotonin reuptake inhibitor combination with a GABAB receptor modulator for treatment of **depression** and other disorders)

IT **Mental disorder**

(post-traumatic stress disorder; serotonin reuptake inhibitor combination with a GABAB receptor modulator for treatment of **depression** and other disorders)

IT 50-49-7, Imipramine 303-49-1, Clomipramine 54739-18-3, Fluvoxamine 54910-89-3, Fluoxetine 59729-33-8, Citalopram 59859-58-4, Femoxetine 61869-08-7, Paroxetine 79617-96-2, Sertraline 83366-66-9, Nefazodone 93413-69-5, Venlafaxine 114012-12-3, Phaclofen 116539-59-4, Duloxetine 117354-64-0, 2-Hydroxysaclofen 119356-77-3, Dapoxetine 123690-78-8, CGP-36742 123690-79-9, CGP-35348 123691-14-5, CGP-46381 125464-42-8, Saclofen 128196-01-0, Escitalopram 139667-74-6, CGP-52432 149184-21-4, CGP-54626 150175-54-5, CGP-55845 160415-07-6, SCH 50911 163521-12-8, Vilazodone 187608-26-0, CGP-62349 212268-87-6, CGP-71982 638211-84-4, CGP 76290 638211-85-5, CGP 76291 638211-86-6, GAS 360

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(serotonin reuptake inhibitor combination with a GABAB receptor modulator for treatment of **depression** and other disorders)

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 209 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2003:1006815 HCAPLUS

DOCUMENT NUMBER: 140:35974

TITLE: Treatment for depression and anxiety by the combination of a PDE IV inhibitor and an antidepressant or an anxiolytic agent

INVENTOR(S): Sobolov-Jaynes, Susan Beth; Schmidt, Christopher Joseph

PATENT ASSIGNEE(S): Pfizer Products Inc., USA

SOURCE: PCT Int. Appl., 62 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003105902	A1	20031224	WO 2003-IB2295	20030605
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2003235631	A1	20031225	US 2003-387060	20030312
CA 2488138	AA	20031224	CA 2003-2488138	20030605
EP 1517707	A1	20050330	EP 2003-727833	20030605
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
BR 2003011903	A	20050607	BR 2003-11903	20030605
PRIORITY APPLN. INFO.:			US 2002-389181P	P 20020617
			WO 2003-IB2295	W 20030605

OTHER SOURCE(S): MARPAT 140:35974

AB The present invention relates to a method of treating depression or anxiety in a mammal, including a human, by administering to the mammal a PDE IV inhibitor in combination with an antidepressant or an anxiolytic agent. It also relates to pharmaceutical compns. containing a pharmaceutically acceptable carrier, a PDE IV inhibitor and an anxiolytic agent or antidepressant.

IC ICM A61K045-06

ICS A61P025-22; A61P025-24

CC 1-11 (Pharmacology)

IT **Mental disorder**

(depression; treatment for depression and anxiety

by combination of a PDE IV inhibitor and an antidepressant or an anxiolytic agent)

IT 50-48-6, Amitriptyline 50-49-7, Imipramine 51-71-8, Phenelzine
 59-63-2, Isocarboxazid 155-09-9, Tranylcypromine 19794-93-5, Trazodone
 24219-97-4, Mianserin 25905-77-5, Minaprine 34911-55-2, Bupropion
 54739-18-3, Fluvoxamine 54910-89-3, Fluoxetine 56775-88-3, Zimelidine
 59729-33-8, Citalopram 61413-54-5 61869-08-7, Paroxetine 72797-41-2,
 Tianeptine 79617-96-2, Sertraline 83366-66-9, Nefazodone 85650-52-8,
 Mirtazapine 92623-85-3, Milnacipran 93413-69-5,
 Venlafaxine 116539-59-4, Duloxetine 121851-47-6 128196-01-0,
 Escitalopram 132210-43-6, Cipamfylline 153259-65-5, Cilomilast
 161178-10-5, Lubazodone hydrochloride 162278-09-3, V-11294A
 162401-32-3, Roflumilast 163521-12-8 180529-63-9 185954-27-2,
 Tofimilast 189940-24-7, Mesopram 190204-71-8 191219-80-4, YM-976
 192767-01-4 192819-27-5, CDC-801 197894-84-1, CI-1044 203382-47-2
 207279-23-0 207993-12-2, Pumafentrine 225100-00-5 256443-69-3
 259744-67-7 260561-48-6 264123-38-8 266997-39-1 298680-25-8
 299157-88-3 300781-85-5 305802-43-1 306759-92-2 308094-69-1
 308285-76-9 308340-86-5 325770-75-0 329306-27-6, BAY 19-8004
 337358-64-2 337359-69-0 337376-23-5 346408-85-3 346441-11-0
 347191-74-6 347885-03-4 348078-16-0 348078-23-9 349494-81-1
 353280-07-6 353458-31-8 358972-78-8 358976-71-3 359001-45-9
 360042-76-8 362718-38-5 413614-82-1 426268-06-6 444659-43-2,
 SCH-351591 491869-01-3 636598-43-1 636598-44-2 636598-45-3
 636598-46-4 636598-47-5 636598-48-6 636598-49-7 636598-50-0

636598-51-1 636598-52-2 636598-53-3 636598-54-4 636598-55-5
636598-56-6 636598-57-7 636598-58-8

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(treatment for depression and anxiety by combination of a PDE IV inhibitor and an antidepressant or an anxiolytic agent)

REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 210 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2003:971889 HCAPLUS

DOCUMENT NUMBER: 140:13076

TITLE: Triple monoamine reuptake

inhibitors for the treatment of chronic pain

INVENTOR(S): Scheel-Krueger, Jorgen; Blackburn-Munro, Gordon John

PATENT ASSIGNEE(S): Neurosearch A/S, Den.

SOURCE: PCT Int. Appl., 20 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003101453	A1	20031211	WO 2003-DK352	20030527
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW			
RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG			
CA 2484482	AA	20031211	CA 2003-2484482	20030527
EP 1513529	A1	20050316	EP 2003-724899	20030527
R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK			
JP 2005531594	T2	20051020	JP 2004-508810	20030527
US 2005239824	A1	20051027	US 2004-515275	20041122
PRIORITY APPLN. INFO.:			DK 2002-832	A 20020530
			WO 2003-DK352	W 20030527

OTHER SOURCE(S): MARPAT 140:13076

AB The present invention relates to the use of triple monoamine reuptake inhibitors for the treatment of chronic pain.

IC ICM A61K031-46

ICS A61P025-04

CC 1-11 (Pharmacology)

IT Fatigue, biological

(chronic fatigue syndrome; triple monoamine reuptake inhibitors for treatment of chronic pain)

IT Mental disorder

(depression, pain associated with; triple monoamine reuptake inhibitors for treatment of chronic pain)

IT Muscle, disease

(fibromyalgia; triple monoamine reuptake

inhibitors for treatment of chronic pain)
 IT Nerve, disease
 Pain
 (neuralgia; **triple monoamine reuptake inhibitors** for treatment of chronic pain)
 IT Monoamines
 RL: BSU (Biological study, unclassified); BIOL (Biological study)
 (**reuptake inhibitors; triple monoamine reuptake inhibitors** for treatment of chronic pain)
 IT Headache
 (tension-type; **triple monoamine reuptake inhibitors** for treatment of chronic pain)
 IT Analgesics
 Anti-inflammatory agents
 Inflammation
 Pain
 (**triple monoamine reuptake inhibitors** for treatment of chronic pain)
 IT 529-17-9D, Tropane, derivs.
 RL: BSU (Biological study, unclassified); BIOL (Biological study)
 (**triple monoamine reuptake inhibitors** for treatment of chronic pain)
 IT 157239-97-9 173667-94-2 173830-08-5 195875-68-4 195875-70-8
 195875-72-0 195875-74-2 195875-76-4 195875-78-6 195875-80-0
 195875-82-2 195875-84-4 195875-87-7 195875-89-9 195875-91-3
 195876-14-3
 RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (**triple monoamine reuptake inhibitors** for treatment of chronic pain)

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 211 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN
 ACCESSION NUMBER: 2003:796467 HCAPLUS
 DOCUMENT NUMBER: 139:297018
 TITLE: Compositions of venlafaxine base for treatment of depression
 INVENTOR(S): Cucala Escoi, Joan; Gallego Luengo, Montserrat; Oosterbaan, Marinus Jacobus Maria; Picha, Frantisek
 PATENT ASSIGNEE(S): Synthon B.V., Neth.
 SOURCE: PCT Int. Appl., 50 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 4
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003082262	A2	20031009	WO 2003-EP3311	20030327
WO 2003082262	A3	20040729		
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW			
RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,			

KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES,
 FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR,
 BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
 EP 1487429 A2 20041222 EP 2003-745289 20030327

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
 IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK

PRIORITY APPLN. INFO.: US 2002-367736P P 20020328
 WO 2003-EP3311 W 20030327

AB The invention relates to a pharmaceutical composition comprising a solid venlafaxine base and a pharmaceutically acceptable excipient, to a process for making a venlafaxine composition, which comprises, e.g., dispersing venlafaxine base in a liquid-phase carrier, and solidifying said liquid phase to form a solid dispersion of venlafaxine, in the form of granules, pellets, and tablets. The composition is useful for treatment of depression using venlafaxine base in an antidepressant amount. For example, venlafaxine base and Compritol ATO 888 were melted at 60°, solidified by cooling and the solid product was granulated. Granules obtained were mixed with microcryst. cellulose, talc and magnesium stearate and compressed into tablets.

IC ICM A61K031-137

ICS A61K009-22

CC 63-6 (Pharmaceuticals)

IT **Mental disorder**

(**depression**; preparation of extended-release venlafaxine comps.
 for treatment of **depression**)

IT 93413-69-5, Venlafaxine

RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological
 study); USES (Uses)

(preparation of extended-release venlafaxine comps. for treatment of
depression)

L91 ANSWER 212 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2003:301059 HCAPLUS

DOCUMENT NUMBER: 138:314606

TITLE: [[2-(amino-3,4-dioxo-1-cyclobuten-1-yl)amino]alkyl]-
 acid derivatives for the treatment of pain

INVENTOR(S): Brandt, Michael Richard; Zaleska, Margaret Maria;
 Moyer, John Allen

PATENT ASSIGNEE(S): Wyeth, John, and Brother Ltd., USA

SOURCE: PCT Int. Appl., 40 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003031416	A2	20030417	WO 2002-US32252	20021009
WO 2003031416	A3	20030814		
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW			
RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF,			

CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

CA 2461348	AA	20030417	CA 2002-2461348	20021009
US 2003114444	A1	20030619	US 2002-267159	20021009
EP 1434588	A2	20040707	EP 2002-789180	20021009
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK				
BR 2002013237	A	20040928	BR 2002-13237	20021009
JP 2005508950	T2	20050407	JP 2003-534400	20021009
NO 2004001378	A	20040528	NO 2004-1378	20040402
PRIORITY APPLN. INFO.:			US 2001-328245P	P 20011010
			WO 2002-US32252	W 20021009

OTHER SOURCE(S): MARPAT 138:314606

AB The invention provides a method for treating pain in a mammal that includes administering I [R1 = H, C1-6 alkyl, C7-12 phenylalkyl; R2 = H, C1-6 alkyl, C2-6 alkenyl, C7-12 phenylalkyl; or R1 and R2 taken together as Z are CH2CH2, CH2C(R6)(R7)CH2, CH2C(R8)(R9)C(R10)(R11)CH2; R6, R8, R10 = H, C1-6 alkyl, OH; R7, R9, R11 = H, C1-6 alkyl; A = C1-6 alkylene, C2-6 alkenylene; X = CO2R3, P(O)(OR4)(OR5), 3,5-dioxo-1,2,4-oxadiazolidin-2-yl, 5-tetrazolyl; R3, R4, R5 = H, C1-6 alkyl], or a pharmaceutically acceptable salt thereof. Also provided are compns. for treating pain containing I.

IC ICM C07D243-00

CC 1-11 (Pharmacology)

Section cross-reference(s): 63

IT **Antidepressants**

(tricyclic; aminodioxocyclobutenyl derivs. for treatment of **pain**, and use with other agents)

IT Biological transport

(uptake, selective **serotonin** or **norepinephrine reuptake inhibitors**; aminodioxocyclobutenyl derivs. for treatment of pain, and use with other agents)

L91 ANSWER 213 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2003:133037 HCAPLUS

DOCUMENT NUMBER: 138:163579

TITLE: Treatment of refractory depression with an opiate antagonist and an antidepressant

INVENTOR(S): Glover, Hillel; Chrisman, Deborah

PATENT ASSIGNEE(S): USA

SOURCE: PCT Int. Appl., 27 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
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WO 2003013524	A1	20030220	WO 2002-US24430	20020802
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR,				

NE, SN, TD, TG
 US 2003087896 A1 20030508 US 2001-925190 20010809
 PRIORITY APPLN. INFO.: US 2001-925190 A 20010809
 AB An antidepressant or a pharmaceutically acceptable salt thereof, and an opiate antagonist or a pharmaceutically acceptable salt thereof, are used to treat refractory depression characterized by dissociation. Two patients scoring high on the Beck Depression Inventory and on the Glover Numbing Scale were treated with the opiate antagonist nalmefene and with SAM-E or venlafaxine as antidepressant.
 IC ICM A61K031-44
 ICS A61K031-55; A61K031-135; A61K031-335
 CC 1-11 (Pharmacology)
 IT **Mental disorder**
 (depression, refractory with dissociation; refractory depression treatment with opiate antagonist and antidepressant)
 IT 50-48-6, Amitriptyline 50-49-7, Imipramine 72-69-5, Nortriptyline 23047-25-8, Lofepamine 29908-03-0, SAM-E 34911-55-2, Bupropion SR 54739-18-3, Fluvoxamine 54910-89-3, Fluoxetine 59729-33-8, Citalopram 61869-08-7, Paroxetine 71620-89-8, Reboxetine 79617-96-2, Sertraline 83366-66-9, Nefazodone 85650-52-8, Mirtazapine 93413-69-5, Venlafaxine
 RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (as antidepressant; refractory depression treatment with opiate antagonist and antidepressant)
 REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 214 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN
 ACCESSION NUMBER: 2003:796113 HCAPLUS
 DOCUMENT NUMBER: 139:296988
 TITLE: Oral compositions of venlafaxine base
 INVENTOR(S): Escoi, Juan Cucala; Luengo, Montserrat Gallego; Oosterbaan, Marinus J. M.; Picha, Frantisek
 PATENT ASSIGNEE(S): Synthon B.V., Neth.
 SOURCE: U.S. Pat. Appl. Publ., 14 pp.
 CODEN: USXXCO
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 4
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2003190352	A1	20031009	US 2003-397353	20030327
PRIORITY APPLN. INFO.:			US 2002-367736P	P 20020328
AB Solid venlafaxine base can be advantageously employed in making pharmaceutical compns., especially extended release compns. For example, tablets were prepared containing venlafaxine base 30.00 mg, silicified microcryst. cellulose 15.00 mg, dicalcium phosphate 44.10 mg, and magnesium stearate 0.90 mg.				
IC ICM A61K031-137				
ICS A61K009-20				
INCL 424465000; 514649000				
CC 63-6 (Pharmaceuticals)				
IT Mental disorder (depression, treatment of; preparation of sustained-release oral compns. of venlafaxine for depression treatment)				
IT 63-42-3, Lactose 473-81-4D, Glyceric acid, polyglycolyzed 9003-39-8,				

Polyvinylpyrrolidone 9004-65-3, HPMC 10103-46-5, Dynafos 18641-57-1,
Glyceryl behenate 93413-69-5, Venlafaxine
RL: **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(preparation of sustained-release oral compns. of venlafaxine for
depression treatment)

L91 ANSWER 215 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2003:315622 HCAPLUS

DOCUMENT NUMBER: 138:314607

TITLE: Therapeutic agent comprising (+)-sibutramine

INVENTOR(S): Cheetham, Sharon C.; Heal, David John

PATENT ASSIGNEE(S): Abbott G.m.b.H. & Co. K.-G., Germany

SOURCE: U.S., 9 pp.

CODEN: USXXAM

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6552087	B1	20030422	US 2000-527659	20000317
US 2003203971	A1	20031030	US 2003-395327	20030324
PRIORITY APPLN. INFO.:			US 1999-125320P	P 19990319
			US 2000-527659	A3 20000317

AB The use of (+)-sibutramine in the treatment of disorders ameliorated by inhibition of neuronal monoamine reuptake, such as depression, obesity, Parkinson's disease, cerebral function disorders, and diabetes, is described.

IC ICM A61K031-36

INCL 514646000; 514909000; 514910000; 514878000; 514879000

CC 1-11 (Pharmacology)

Section cross-reference(s): 63

IT **Mental disorder**

(**depression**; affinity of sibutramine enantiomer for monoamine reuptake sites in rat and human brain and treatment of **depression**, obesity and other disorders)

IT 154752-44-0, (+)-Sibutramine 154752-45-1,
(+)-Sibutramine hydrochloride

RL: **PAC (Pharmacological activity)**; PRP (Properties); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)

(affinity of sibutramine enantiomer for monoamine reuptake sites in rat and human brain and treatment of **depression**, obesity and other disorders)

REFERENCE COUNT: 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 216 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2003:941631 HCAPLUS

DOCUMENT NUMBER: 139:391248

TITLE: Duloxetine in the long-term treatment of major depressive disorder

AUTHOR(S): Raskin, Joel; Goldstein, David J.; Mallinckrodt, Craig H.; Ferguson, Margaret B.

CORPORATE SOURCE: Lilly Research Laboratories, Eli Lilly Canada Inc., Scarborough, ON, M1N 2E8, Can.

SOURCE: Journal of Clinical Psychiatry (2003), 64(10), 1237-1244

CODEN: JCLPDE; ISSN: 0160-6689

PUBLISHER: Physicians Postgraduate Press, Inc.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Background: Depression is a chronic recurring disorder and guidelines recommend long-term therapy. This clin. trial evaluated the long-term (1 yr) safety and efficacy of duloxetine, a dual reuptake inhibitor of serotonin and norepinephrine, in patients with DSM-IV major depressive disorder. Method: This was an open-label, 52-wk, multinational clin. trial in outpatients (age \geq 18 yr) who received duloxetine at 80 mg/day (administered 40 mg twice daily) to 120 mg/day (administered 60 mg twice daily) for up to 1 yr. Results: A total of 1279 patients had postbaseline data. Of these, 520 were exposed to duloxetine for at least 360 days, yielding approx. 808 patient-years of total exposure. Mean changes in Clin. Global Impressions-Severity of Illness scale (CGI-S) score, 17-item Hamilton Rating Scale for Depression total score and subfactor scores, Beck Depression Inventory-II score, and Sheehan Disability Scale score and mean Patient Global Impression-Improvement scale (PGI-I) scores all showed highly significant ($p < .001$) improvements at all assessment times. The estimated probabilities of improvement in CGI-S and PGI-I scores at week 1 were 40.4% and 59.2%, resp., and at week 2 were 70.0% and 78.3%. The estimated probabilities of remission at weeks 6, 28, and 52 were 50.8%, 75.6%, and 81.8%, resp. Adverse events led to discontinuation in 218 patients (17.0%). The most frequent specific events leading to discontinuation were nausea (1.5%), somnolence (1.4%), vomiting (0.9%), hypomania (0.8%), pregnancy (0.8%), dizziness (0.6%), insomnia (0.6%), and hypertension (0.5%). Treatment-emergent adverse events that were reported by $> 10\%$ of patients included nausea, insomnia, headache, somnolence, dry mouth, dizziness, constipation, sweating increase, anxiety, diarrhea, and fatigue. Most events occurred early in the study. Of those events that first occurred or worsened after discontinuation, only dizziness (8.3%) occurred in more than 5% of patients. Mean changes from baseline to last observation for standing and supine pulse were less than 2 b.p.m. Mean changes in blood pressure (< 1.0 mm Hg), corrected QT interval (< 1 ms), and body weight (2.4 kg [5.3 lb])

were

not clin. significant. Laboratory analyses varied across visits, and mean changes after 52 wk were generally close to zero. The incidence of laboratory values above or below normal limits at any time during treatment was low. Conclusion: Duloxetine was effective, safe, and well tolerated in the long-term treatment of major depression at a dose of 80 to 120 mg/day in this study.

CC 1-11 (Pharmacology)

IT **Mental disorder**

(major depression; efficacy of duloxetine in long-term treatment of patients with major depressive disorder)

IT 116539-59-4, Duloxetine

RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(efficacy of duloxetine in long-term treatment of patients with major depressive disorder)

REFERENCE COUNT: 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 217 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2003:626067 HCAPLUS

DOCUMENT NUMBER: 140:157221

TITLE: Selective serotonin reuptake inhibitors combined with venlafaxine in depressed patients who had partial

response to venlafaxine: four cases
AUTHOR(S): Gonul, Ali Saffet; Akdeniz, Fisun; Donat, Ozlem; Vahip, Simavi
CORPORATE SOURCE: School of Medicine, Department of Psychiatry, Affective Disorders Unit, Ege University, Izmir, 35100, Turk.
SOURCE: Progress in Neuro-Psychopharmacology & Biological Psychiatry (2003), 27(5), 889-891
CODEN: PNPPD7; ISSN: 0278-5846
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB One third of depressive patients show partial or no response to antidepressant treatment. With partial or nonresponders, treatment strategies are as follows: switching to another antidepressant, augmenting with other psychotropic agents, or combining antidepressants. There are no data in the literature about the pos. effect of combining venlafaxine with selective serotonin reuptake inhibitors (SSRIs). The presented cases had been on at least two different classes of antidepressant medication (or combination of antidepressants) for an adequate time and dose. They showed only a partial response to high dose of venlafaxine but improved after the addition of an SSRI (sertraline, citalopram, or paroxetine) to venlafaxine. The combination treatment was well tolerated in all of the cases.
CC 1-11 (Pharmacology)
IT **Mental disorder**
(**depression**; selective serotonin reuptake inhibitors combined with venlafaxine in depressed patients who had partial response to venlafaxine)
IT 59729-33-8, Citalopram 61869-08-7, Paroxetine 79617-96-2, Sertraline 93413-69-5, Venlafaxine
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study);
USES (Uses)
(selective serotonin reuptake inhibitors combined with venlafaxine in **depressed** patients who had partial response to venlafaxine)
REFERENCE COUNT: 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 218 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:760141 HCAPLUS
DOCUMENT NUMBER: 139:301936
TITLE: Probing the safety of medications in the frail elderly: evidence from a randomized clinical trial of sertraline and venlafaxine in depressed nursing home residents
AUTHOR(S): Oslin, David W.; Ten Have, Thomas R.; Streim, Joel E.; Datto, Catherine J.; Weintraub, Daniel; DiFilippo, Suzanne; Katz, Ira R.
CORPORATE SOURCE: Section of Geriatric Psychiatry, Department of Psychiatry, University of Pennsylvania, Philadelphia, PA, USA
SOURCE: Journal of Clinical Psychiatry (2003), 64(8), 875-882
CODEN: JCLPDE; ISSN: 0160-6689
PUBLISHER: Physicians Postgraduate Press, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB In nursing home residents and other frail elderly patients, old age and potential drug-drug and drug-disease interactions may affect the relative

safety and efficacy of medications. The purpose of this study was to examine the efficacy and tolerability of venlafaxine and sertraline for the treatment of depression among nursing home residents. The study was a 10-wk randomized, double-blind, controlled trial of venlafaxine (doses up to 150 mg/day) vs. sertraline (doses up to 100 mg/day) among 52 elderly nursing home residents with a DSM-IV depressive disorder and, at most, moderate dementia. The primary measure of outcome was the Hamilton Rating Scale for Depression (HAM-D). Adverse events were monitored and recorded systematically during the trial. Twelve subjects were discontinued due to serious adverse events (SAE), 5 were discontinued due to other significant side effects, and 2 withdrew consent. Tolerability estimated by the time to termination was lower for venlafaxine than sertraline for serious adverse events (log rank statistic = 5.28, $p = .022$), for serious adverse events or side effects (log rank statistic = 8.08, $p = .005$), or for serious adverse events, side effects, or withdrawal of consent (log rank statistic = 10.04, $p = .002$). Mean (SD) HAM-D scores at baseline were 20.2 (3.4) for sertraline and 20.3 (3.7) for venlafaxine; intent-to-treat endpoint HAM-D scores were 12.2 (5.1) and 15.7 (6.2) ($F = 3.45$; $p = .069$). There were no differences in categorical responses for the intent-to-treat sample or completers. In this frail elderly population, venlafaxine was less well tolerated and, possibly, less safe than sertraline without evidence for an increase in efficacy. This unexpected finding demonstrates the need for systematic research on the safety of drugs in the frail elderly.

CC 1-11 (Pharmacology)

IT **Mental disorder**

(depression; sertraline and venlafaxine in depressed frail elderly)

IT 79617-96-2, Sertraline 93413-69-5, Venlafaxine

RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(sertraline and venlafaxine in depressed frail elderly)

REFERENCE COUNT: 49 THERE ARE 49 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 219 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2004:79523 HCAPLUS

DOCUMENT NUMBER: 140:139358

TITLE: Milnacipran and pindolol: a randomized trial of reduction of antidepressant latency

AUTHOR(S): Isaac, Michael T.; Isaac, Maria B.; Gallo, Fidel; Tournoux, Alan

CORPORATE SOURCE: South London and Maudsley NHS Trust, Psychopharmacology Evaluation Unit, University Hospital Lewisham, London, SE13 6LH, UK

SOURCE: Human Psychopharmacology (2003), 18(8), 595-601
CODEN: HUPSEC; ISSN: 0885-6222

PUBLISHER: John Wiley & Sons Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Background: New, better tolerated and faster treatments for depression are needed. Patients are understandably unhappy with having to wait 3 to 4 wk for a response to an antidepressant, while experiencing side effects almost immediately. This frequently has an adverse effect on compliance and engagement with treatment. Aims: The primary objective was to assess the activity of pindolol on the onset of antidepressive response of milnacipran. The secondary objective was to assess the number of responders among the patients who received milnacipran and pindolol vs. patients who

received milnacipran and placebo. The tertiary objective was to evaluate the safety of milnacipran and pindolol vs. milnacipran and placebo. Method: Randomized, double-blind, placebo-controlled study over 42 days. Setting: Inner city London community mental health teams. Participants: 80 patients were selected and gave written consent to treatment, 78 were randomized (39 in each group) and evaluated for safety (intention-to-treat, ITT, safety data set), 77 (ITT efficacy data set), and 64 (per protocol, PP, data set) were evaluated for efficacy. The mean age was 31.9 for the pindolol group and 32.3 for the placebo. Intervention: All patients received milnacipran 50 mg twice a day plus either pindolol 2.5 mg (the 'pindolol group') or matching placebo (the 'placebo group') three times a day. Outcome measures: The main efficacy variable was the Montgomery-Asberg depression rating scale (MADRS) score at days 0, 4, 7, 10, 14, 21, 28, 42 on PP data set in an observation carried (OC) approach. Secondary efficacy variables were clin. global impression (global improvement) and Hamilton depression rating scale (HDRS). Results: Improvement in MADRS total score was greater in the pindolol group than in the placebo group from day 7 ($p = 0.03$). Responder rates in the clin. global impression were 97.2% for the pindolol group and 60.6% for the placebo group. The treatment was well tolerated with the most common side effects being nausea (28.2%; 35.9%), vomiting (7.7%; 23.1%), hot flushes (15.4%; 5.1%) and sweating (12.8%; 12.8%). Conclusion: The milnacipran and pindolol combination is safe, well tolerated and efficacious in major depression, and represents a rational strategy for the possible acceleration or potentiation of antidepressant action.

CC 1-11 (Pharmacology)

IT **Mental disorder**

(unipolar **depression**; milnacipran/pindolol combination and reduction of antidepressant latency for patients with unipolar **depression**)

IT 13523-86-9, Pindolol **92623-85-3**, Milnacipran

RL: ADV (Adverse effect, including toxicity); **PAC (Pharmacological activity)**; **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)

(milnacipran/pindolol combination and reduction of antidepressant latency for patients with unipolar **depression**)

REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 220 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2003:904129 HCAPLUS

DOCUMENT NUMBER: 139:374878

TITLE: Effect of pindolol and milnacipran versus milnacipran and placebo on plasma prolactin and adrenocorticotrophic hormone in depressed subjects

AUTHOR(S): Isaac, Maria B.; Isaac, Michael T.

CORPORATE SOURCE: South London and Maudsley NHS Trust, Gresham Psychiatric Intensive Care Unit, Bethlem Royal Hospital, Beckenham, Kent, BR3 3BX, UK

SOURCE: Human Psychopharmacology (2003), 18(7), 569-574
CODEN: HUPSEC; ISSN: 0885-6222

PUBLISHER: John Wiley & Sons Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Evidence that pindolol accelerates the action of antidepressants has been contradictory, and it is not clear why. The present study analyses the relationship between plasma prolactin (PRL) and ACTH levels and changes in relation to a milnacipran and pindolol combination vs. milnacipran plus

placebo. Eighty depressed patients agreed to take part in a double-blind randomized trial of milnacipran plus pindolol or placebo. Fifty-eight of them agreed to also take measures of ACTH and PRL levels. ACTH and PRL plasma levels were estimated on days 0 and 42 of the 6-wk study. Age, gender and time of blood collection were recorded for each individual. The Montgomery-Asberg depression rating scale (MADRS) was used to measure the response to treatment. The patients were grouped into those with higher vs. lower basal ACTH levels using the median of the sample (25 ng/l). There were statistical differences in MADRS scores between the treatment groups on day 42. There were correlations between PRL levels on days 0 and 42; age and PRL levels on day 0; time of the PRL sample and the PRL levels on day 0 and day 42; ACTH and PRL levels on day 42. Regression anal. of the 58 patients showed that on day 0, PRL levels were dependent on the ACTH plasma levels on day 0, the time of the collection of the blood sample and the age. On day 42, the PRL levels were dependent on the ACTH levels and the time of the blood collection but not on the age. Patients with lower baseline ACTH levels on day 0 displayed a better clin. outcome when taking the combination of milnacipran and pindolol as shown in the differences in MADRS on day 42. The same group of patients showed lower PRL levels on day 42. ACTH plasma levels at baseline or screening may help to predict the response to antidepressant treatment.

CC 1-11 (Pharmacology)

IT **Mental disorder**

(**depression**; effect of pindolol and milnacipran vs. milnacipran and placebo on plasma prolactin and ACTH in depressed subjects)

IT 13523-86-9, Pindolol 92623-85-3, Milnacipran

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(effect of pindolol and milnacipran vs. milnacipran and placebo on plasma prolactin and ACTH in **depressed** subjects)

REFERENCE COUNT: 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 221 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2003:780766 HCAPLUS

DOCUMENT NUMBER: 139:332986

TITLE: Differential period of onset of action of fluvoxamine, paroxetine and milnacipran for depression

AUTHOR(S): Morishita, Shigeru; Arita, Seizaburo

CORPORATE SOURCE: Department of Psychiatry, Kawasaki Medical School, Kurashiki, Okayama, Japan

SOURCE: Human Psychopharmacology (2003), 18(6), 479-482
CODEN: HUPSEC; ISSN: 0885-6222

PUBLISHER: John Wiley & Sons Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Introduction: Selective serotonin reuptake inhibitors (SSRIs) and dual serotonin and noradrenaline reuptake inhibitors (SNRIs) are the most commonly prescribed class of antidepressants, yet it is not known whether one is superior to another. Aims: The purpose of this clin. practice was to compare the periods of onset of action of fluvoxamine, paroxetine and milnacipran. Methods: A retrospective cohort anal. was carried out among out-patients with depression treated in the Department of Psychiatry, Kawasaki Medical School Hospital, Kurashiki, Japan, in 2000 and 2001. A total of 206 patients receiving fluvoxamine, paroxetine and milnacipran were identified. Results: The cumulative percentage of responders receiving milnacipran reached over 80% after 4 wk, but it did reach this level for fluvoxamine or paroxetine until after 6 wk. Conclusions: The

differential period of onset of action should help guide clinicians in determining a suitable duration of antidepressants for depression.

CC 1-11 (Pharmacology)

IT **Mental disorder**

(**depression**; differential period of onset of action of fluvoxamine, paroxetine and milnacipran for patients with **depression**)

IT 54739-18-3, Fluvoxamine 61869-08-7, Paroxetine 92623-85-3, Milnacipran

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(differential period of onset of action of fluvoxamine, paroxetine and milnacipran for patients with **depression**)

REFERENCE COUNT: 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 222 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2004:44717 HCAPLUS

DOCUMENT NUMBER: 140:105151

TITLE: Antidepressant monotherapy for bipolar type II major depression

AUTHOR(S): Amsterdam, Jay D.; Brunswick, David J.

CORPORATE SOURCE: Department of Psychiatry, Depression Research Unit, University of Pennsylvania School of Medicine, Philadelphia, PA, USA

SOURCE: Bipolar Disorders (2003), 5(6), 388-395

CODEN: BDIIAU; ISSN: 1398-5647

PUBLISHER: Blackwell Publishing Ltd.

DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

AB Objectives: Bipolar type II (BP II) disorder is thought to be distinct from BP I disorder on genetic and biol. grounds, and it is not merely a milder form of the illness. It affects 1.5-2.5% of the US adult population, and is characterized by highly recurrent depressive episodes with a substantial morbidity from alcoholism and non-affective psychopathol., and a higher suicide rate than either BP I or unipolar depression. Treatment recommendations for BP II depression are based upon concerns over drug-induced manic-switch episodes, and suggest using either a mood stabilizer alone or a combination of an SSRI plus a mood stabilizer. Recent evidence, however, indicates that the rate of manic switch episodes may be modest in BP II patients. Recent studies have provided evidence that antidepressant monotherapy may be an effective initial and long-term treatment for BP II major depression with a low manic-switch rate. Methods: In this article, the authors review the recent literature on BP II disorder, with a focus on the treatment of BP II major depression. Results: The authors present a summary of data from recent studies by their group and others indicating that antidepressant monotherapy for BP II depression may be safe and effective with a low manic-switch rate. Conclusion: Antidepressant monotherapy may be beneficial for some patients with BP II major depression.

CC 1-11 (Pharmacology)

IT **Mental disorder**

(bipolar disorder; antidepressant monotherapy for bipolar type II major **depression**)

IT **Mental disorder**

(major **depression**; antidepressant monotherapy for bipolar type II major **depression**)

IT 54910-89-3, Fluoxetine 93413-69-5, Venlafaxine

RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological

activity); THU (Therapeutic use); BIOL (Biological study);
USES (Uses)
(antidepressant monotherapy for bipolar type II major
depression)

REFERENCE COUNT: 62 THERE ARE 62 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 223 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2003:320605 HCAPLUS

DOCUMENT NUMBER: 139:47029

TITLE: Depression-free days as a summary measure of the
temporal pattern of response and remission in the
treatment of major depression: A comparison of
venlafaxine, selective serotonin reuptake inhibitors,
and placebo

AUTHOR(S): Mallick, Rajiv; Chen, Jiuling; Entsuah, A. Richard;
Schatzberg, Alan F.

CORPORATE SOURCE: Department of Psychiatry and Behavioral Sciences,
School of Medicine, Stanford University, Stanford, CA,
94305-5717, USA

SOURCE: Journal of Clinical Psychiatry (2003), 64(3), 321-330
CODEN: JCLPDE; ISSN: 0160-6689

PUBLISHER: Physicians Postgraduate Press, Inc.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB This article develops and applies depression-free days (DFDs) as a summary measure of the temporal pattern of response and remission in a comparison of venlafaxine (a dual-action serotonin norepinephrine reuptake inhibitor) with selective serotonin reuptake inhibitors (SSRIs) and placebo. Weekly data on the 17-item Hamilton Rating Scale for Depression (HAM-D-17) from 2046 patients with DSM-III-R/IV-established moderate-to-severe major depression, participating in 1 of 8 randomized, double-blind, controlled studies that compared venlafaxine with an SSRI (fluoxetine, paroxetine, or fluvoxamine) or with both placebo and an SSRI, were used to estimate DFDs. Maximum DFDs were imputed to maintained HAM-D-17 scores ≤ 7 (asymptomatic depression) over time, min. DFDs to persistent HAM-D-17 scores ≥ 15 (acutely symptomatic depression), and prorated DFDs to intermediate HAM-D-17 scores. A secondary construct was developed to test sensitivity to a less stringent upper threshold of acutely symptomatic depression (HAM-D-17 score ≥ 22). Using a tertiary construct, sensitivity to a more stringent lower threshold representing elimination of residual symptoms was also evaluated. The construct validity of the primary and the secondary DFDs measures was assessed in terms of their correlation with sustained low clin. global severity of illness (scores of 1 or 2 on the Clin. Global Impressions-Severity of Illness scale). For each construct, DFDs were compared across the 3 treatment groups and corresponding effect sizes were generated. Overall, sustained low clin. global severity of illness was associated with 38.3 median (interquartile range, 29.8 to 44.2) DFDs relative to 5.7 (interquartile range, 0 to 20.6) median DFDs associated with nonsustained low clin. global severity; similar differences emerged in terms of sustained asymptomatic depression. The venlafaxine group (N = 851) experienced a median of 18.8 (interquartile range, 0.4 to 34.6) DFDs compared with a median of 13.6 (interquartile range, 0 to 29.8) DFDs in the SSRI group (N = 749) and 7.4 (interquartile range, 0 to 26.2) DFDs in the placebo group (N = 446) (p < .0001 overall; venlafaxine vs. SSRIs, p = .0015, effect size = 0.2; venlafaxine vs. placebo, p < .0001, effect size = 0.4; and SSRIs vs. placebo, p = .0007, effect size = 0.2). The secondary and tertiary DFDs constructs yielded similar, albeit narrower, differences in all comparisons. The construct

of DFDs was found to be a useful summary measure of sustained remission. Active treatments were associated with more DFDs than placebo, and venlafaxine with more DFDs than SSRIs, consistent with corresponding differences in sustained remission.

CC 1-11 (Pharmacology)

IT **Mental disorder**

(**depression**; **depression-free days** as summary measure of temporal pattern of response and remission in comparison of venlafaxine and SSRI treatment of major **depression**)

IT 54739-18-3, Fluvoxamine 54910-89-3, Fluoxetine 61869-08-7, Paroxetine 93413-69-5, Venlafaxine

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(**depression-free days** as summary measure of temporal pattern of response and remission in comparison of venlafaxine and SSRI treatment of major **depression**)

REFERENCE COUNT: 53 THERE ARE 53 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 224 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2003:553090 HCAPLUS

DOCUMENT NUMBER: 139:191279

TITLE: Milnacipran plasma levels and antidepressant response in Japanese major depressive patients

AUTHOR(S): Higuchi, Hisashi; Yoshida, Keizo; Takahashi, Hitoshi; Naito, Shingo; Kamata, Mitsuhiro; Ito, Kenichi; Sato, Kazuhiro; Tsukamoto, Kei; Shimizu, Tetsuo; Nakanishi, Mamoru; Hishikawa, Yasuo

CORPORATE SOURCE: Omagari City Hospital, Iida, Omagari, Akita, 014-0067, Japan

SOURCE: Human Psychopharmacology (2003), 18(4), 255-259

CODEN: HUPSEC; ISSN: 0885-6222

PUBLISHER: John Wiley & Sons Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The relationship between antidepressant effects and plasma levels of milnacipran was studied in 49 cases of major depression without psychotic features during 6 wk of milnacipran treatment. The daily dose of milnacipran was 50 mg/day for the first week, and up to 100 mg/day thereafter. Depressive symptoms were evaluated by the Montgomery and Asberg depression rating scale (MADRS) before treatment and at 1, 2, 4 and 6 wk after the beginning of this study. Thirty-four patients (69.4%) were responders (defined as a 50% or greater decrease in the baseline MADRS score). Significant differences of MADRS scores were seen from 1 wk after the beginning of this study ($p = 0.004$, unpaired t-test) between responders and nonresponders. The mean plasma milnacipran level of responders, 82.0 ± 29.4 ng/mL was similar to that of non-responders, 78.6 ± 23.1 ng/mL; there was no significant difference between responders and nonresponders. Neither a significant linear nor a curvilinear relationship was obtained between the final MADRS score and the plasma levels of milnacipran. Although there was no significant relationship between the plasma levels of milnacipran and the antidepressant response, milnacipran should be considered an efficacious agent in the treatment of major depressive patients.

CC 1-11 (Pharmacology)

IT **Mental disorder**

(**major depression**; milnacipran plasma levels and antidepressant response in Japanese major depressive patients)

IT 92623-85-3, Milnacipran

RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(milnacipran plasma levels and antidepressant response in Japanese major depressive patients)

REFERENCE COUNT: 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 225 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2003:769945 HCAPLUS

DOCUMENT NUMBER: 140:229131

TITLE: Addition of a dopamine agonist, cabergoline, to a serotonin-noradrenalin reuptake inhibitor, milnacipran as a therapeutic option in the treatment of refractory depression: Two Case Reports

AUTHOR(S): Takahashi, Hitoshi; Yoshida, Keizo; Higuchi, Hisashi; Shimizu, Tetsuo; Inoue, Takeshi; Koyama, Tsukasa

CORPORATE SOURCE: Department of Neuro-Psychiatry, Akita University School of Medicine, Akita, Japan

SOURCE: Clinical Neuropharmacology (2003), 26(5), 230-232
CODEN: CLNEDB; ISSN: 0362-5664

PUBLISHER: Lippincott Williams & Wilkins

DOCUMENT TYPE: Journal

LANGUAGE: English

AB We illustrate 2 patients with depression who attained dramatic improvement of energy loss and fatigue when treated with cabergoline, a dopamine agonist, and milnacipran, a serotonin-noradrenalin reuptake inhibitor. Although the biol. basis of energy, motivation, and fatigue in association with depression remains unknown, some reports suggest that the decrease of noradrenalin and dopamine in the brain are particularly related to these symptoms. Therefore, treatment strategy that enhances these two monoamine neurotransmissions may be appropriate for getting a boost in energy and eliminating fatigue in patients with depression. These cases suggest that further studies are warranted to confirm the potential benefit of this strategy in the treatment of patients with depression who failed to attain complete remission due to residual symptoms including energy loss and fatigue refractory to previous treatments.

CC 1-11 (Pharmacology)

IT **Mental disorder**

(**depression**; addition of dopamine agonist cabergoline to serotonin-noradrenalin reuptake inhibitor milnacipran in treatment of **depression**)

IT 81409-90-7, Cabergoline 92623-85-3, Milnacipran

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(addition of dopamine agonist cabergoline to serotonin-noradrenalin reuptake inhibitor milnacipran in treatment of **depression**)

REFERENCE COUNT: 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 226 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2003:864974 HCAPLUS

DOCUMENT NUMBER: 139:358658

TITLE: Quality of life in 833 outpatients with major depression treated with open-label venlafaxine extended release: an observational 24-week study

AUTHOR(S): Cervera-Enguix, Salvador; Soutullo, Cesar A.;

Landecho, Ignacio; Murillo-Jelsbak, Ricardo

CORPORATE SOURCE: The Quality of Life Group, Department of Psychiatry &

Medical Psychology, Clinica Universitaria, University of Navarra, Pamplona, Spain

SOURCE: International Journal of Psychiatry in Clinical Practice (2003), 7(3), 193-197
CODEN: IJPCFZ; ISSN: 1365-1501

PUBLISHER: Taylor & Francis

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Background: Quality of Life (QoL) assessments are common in medicine and, recently, in psychiatry, mostly in patients with chronic mental illness. We evaluated QoL in depressed outpatients treated with venlafaxine-XR over a period of 24 wk. Method: We evaluated 833 patients with DSM-IV major depression using the Hamilton Depression Rating Scale (HAM-D), the Hamilton Anxiety Rating Scale (HAM-A), the Montgomery-Asberg Depression Rating Scale (MADRS), and the QoL in Depression Scale (QLDS). The patients received venlafaxine-XR and we evaluated them after 4, 8, and 24 wk of treatment. Results: HAM-D scores decreased from a baseline of 24.6 ± 6.3 to 6.0 ± 5.5 (mean \pm SD; $P < 0.0001$) after 24 wk. HAM-A scores decreased from a baseline of 32.3 ± 7.9 to 6.8 ± 6.8 ($P < 0.0001$) after 24 wk. QLDS scores decreased from a baseline of 25.8 ± 5.8 to 6.6 ± 7.5 ($P < 0.0001$) after 24 wk, indicating improvement in QoL. The response after 4 wk was also significant and continued improving during the study. Venlafaxine-XR was shown to be safe and well tolerated. Discussion: Open-label venlafaxine-XR was safe, effective, well tolerated, and improved not only depression and anxiety symptoms, but also QoL, in outpatients with major depression. This study has the limitations of any non-randomized, non-blinded multiple-site clin. trial.

CC 1-11 (Pharmacology)
Section cross-reference(s): 63

IT **Mental disorder**
(major **depression**; effect of venlafaxine extended release treatment on quality of life in patients with major **depression**)

IT **93413-69-5, Venlafaxine**
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study);
USES (Uses)
(effect of venlafaxine extended release treatment on quality of life in patients with major **depression**)

REFERENCE COUNT: 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 227 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2004:84413 HCAPLUS

DOCUMENT NUMBER: 140:335837

TITLE: Effect of EGb and venlafaxine in the expression of BDNF and behavioral changes in rats of depression model

AUTHOR(S): Qin, Xiaosong; Jin, Kuihe

CORPORATE SOURCE: Department of Medical Laboratory, the 2nd Affiliated Hospital, China Medical University, Shenyang, 110004, Peop. Rep. China

SOURCE: Zhongguo Shenjing Jingshen Jibing Zazhi (2003), 29(3), 187-189
CODEN: ZSJZEH; ISSN: 1002-0152

PUBLISHER: Zhongzhan Yike Daxue Qikan Zhongxin

DOCUMENT TYPE: Journal

LANGUAGE: Chinese

AB The pathogenesis of depression and the effects of EGb and venlafaxine on

the therapy of depression were studied. Rats were treated with chronic and comprehensive stress to form depression model. The immunohistochem. method was used to detect the expression of brain-derived neurotrophic factor (BDNF) in hippocampus CA3 neurons of rats treated with different drugs. The behavioral changes of these rats were also examined. The expression of BDNF in hippocampal CA3 neurons in rat of depression model decreased, exploring behavior decreased and defecation increased significantly. The rats treated with EGb and venlafaxine showed increased expression of BDNF and exploring behaviors and decreased defecations. Brain damage occurred in rats treated with chronic and comprehensive stress. It was suggested that EGb and venlafaxine might help relief depression by protecting the brain from being damaged.

CC 11-8 (Plant Biochemistry)

Section cross-reference(s): 1

IT **Mental disorder**

(**depression**; effect of EGb and venlafaxine in expression of BDNF and behavioral changes in rats of **depression** model)

IT 99300-78-4, Venlafaxine hydrochloride

RL: BSU (Biological study, unclassified); THU (Therapeutic use);

BIOL (Biological study); USES (Uses)

(effect of EGb and venlafaxine in expression of BDNF and behavioral changes in rats of **depression** model)

L91 ANSWER 228 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2003:977100 HCAPLUS

DOCUMENT NUMBER: 141:17385

TITLE: Expression of cAMP response element-binding protein in major depression before and after antidepressant treatment

AUTHOR(S): Lai, I-Ching; Hong, Chen-Jee; Tsai, Shih-Jen

CORPORATE SOURCE: Department of Psychiatry, Yuli Veterans Hospital, Taichung, Peop. Rep. China

SOURCE: Neuropsychobiology (2003), 48(4), 182-185

CODEN: NPBYAL; ISSN: 0302-282X

PUBLISHER: S. Karger AG

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Antidepressants usually take weeks to exert significant therapeutic effects. This lag phase is suggested to be due to neural plasticity, which may be mediated by the coupling of receptors to their resp. intracellular signal transduction pathways. Phosphorylated cAMP response element-binding protein (CREB), a downstream target of the cAMP signaling pathway, has been reported to be a mol. state marker for the response to antidepressant treatment in patients with major depressive disorder (MDD). In order to explore the role of CREB expression in MDD, we used quant. reverse transcriptase-polymerase chain reaction to quantify CREB mRNA of the peripheral lymphocytes obtained from 21 MDD patients, before and after antidepressant treatment, and 21 normal controls. The results revealed no significant difference of CREB expression between untreated MDD patients and normal controls. However, after 8 wk of antidepressant treatment, CREB expression was significantly decreased in MDD patients ($p = 0.025$). The CREB change is not associated with the types of antidepressants and therapeutic response.

CC 1-11 (Pharmacology)

IT **Mental disorder**

(major **depression**; effect of antidepressant treatment on cAMP response element-binding protein expression in major **depression**)

IT 54910-89-3, Fluoxetine 93413-69-5, Venlafaxine

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(effect of antidepressant treatment on cAMP response element-binding protein expression in major depression)

REFERENCE COUNT: 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 229 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2003:947349 HCAPLUS

DOCUMENT NUMBER: 140:624

TITLE: Efficacy and safety of venlafaxine ER vs. amitriptyline ER in patients with major depression of moderate severity

AUTHOR(S): Sauer, Heinrich; Huppertz-Helmhold, Sabine; Dierkes, Wilfried

CORPORATE SOURCE: Department of Psychiatry, Friedrich-Schiller University, Jena, Germany

SOURCE: Pharmacopsychiatry (2003), 36(5), 169-175

CODEN: PHRMEZ; ISSN: 0176-3679

PUBLISHER: Georg Thieme Verlag

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Introduction: A double-blind, randomized phase-III study was conducted with the aim to compare the efficacy and safety of venlafaxine ER (extended release) with that of amitriptyline ER in moderately depressed outpatients. Methods: Patients with major depression of moderate severity, HAM-D (Hamilton Depression scale, 21 items) score 20-26, were given a six-week double-blind treatment with venlafaxine ER and amitriptyline ER in a doses of 75 mg each, which could be increased to 150mg, if necessary. Efficacy was assessed using HAM-D and CGI (clin. global impression) scores. Safety anal. was carried out using the HAM-D item 3 to assess suicidality, the d2 test to evaluate attention and drug screening for benzo-diazepines. Adverse events were recorded at each visit. Results: 160 patients were randomized. There were 151 patients available for anal. in the intent-to-treat (ITT) population. The according-to-protocol (ATP) population consisted of 117 patients, with 60 patients in the venlafaxine ER group and 57 in the amitriptyline ER (extended release) group. The non-inferiority of venlafaxine ER compared to amitriptyline ER with reference to the primary efficacy parameter, the change of HAM-D total score, could be proven in both the ITT population and the ATP population. There were no significant differences between groups in the HAM-D response rates and the CGI scores of items 1 (severity) and 2 (improvement). Venlafaxine ER showed a more favorable safety profile than amitriptyline ER: adverse drug reactions were less frequent under venlafaxine ER than under amitriptyline ER. Most of the discontinuations in the amitriptyline ER group were due to dry mouth. The d2 test showed greater improvement of performance under venlafaxine ER. Discussion: In this study with patients treated for major depression of moderate severity, the non-inferiority of venlafaxine ER compared to amitriptyline ER with respect to the chosen efficacy parameter could be demonstrated. Venlafaxine ER showed a more favorable safety profile than amitriptyline ER.

CC 1-11 (Pharmacology)

Section cross-reference(s): 63

IT Mental disorder

(major depression; comparison of efficacy of venlafaxine ER (extended release) vs. amitriptyline ER in patients with major depression of moderate severity)

IT 50-48-6, Amitriptyline 93413-69-5, Venlafaxine

RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(comparison of efficacy of venlafaxine ER (extended release) vs. amitriptyline ER in patients with major depression of moderate severity)

REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 230 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2003:499004 HCAPLUS

DOCUMENT NUMBER: 140:53190

TITLE: Alterations of serum levels of brain-derived neurotrophic factor (BDNF) in depressed patients with or without antidepressants

AUTHOR(S): Shimizu, Eiji; Hashimoto, Kenji; Okamura, Naoe; Koike, Kaori; Komatsu, Naoya; Kumakiri, Chikara; Nakazato, Michiko; Watanabe, Hiroyuki; Shinoda, Naoyuki; Okada, Sin-ichi; Iyo, Masaomi

CORPORATE SOURCE: Graduate School of Medicine, Department of Psychiatry, Chiba University, Chiba, 260-8670, Japan

SOURCE: Biological Psychiatry (2003), 54(1), 70-75

CODEN: BIPCBF; ISSN: 0006-3223

PUBLISHER: Elsevier Inc.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Because researchers have reported that antidepressants increase the expression of brain-derived neurotrophic factor (BDNF) in the rat hippocampus, we investigated whether serum BDNF levels may be used as a putative biol. marker for major depressive disorders (MDD). We measured serum BDNF in the following three groups: antidepressant-naive patients with MDD (n = 16), antidepressant-treated patients with MDD (n = 17), and normal control subjects (n = 50). Patients were evaluated using the Hamilton Rating Scale for Depression (HAM-D). Serum BDNF was assayed with the sandwich ELISA method. We found that serum BDNF was significantly lower in the antidepressant-naive group (mean, 17.6 ng/mL; SD, 9.6) than in the treated (mean, 30.6 ng/mL; SD, 12.3; p = .001) or in the control group (mean, 27.7 ng/mL; SD, 11.4; p = .002). There was a significant neg. correlation (r = -.350, z = -2.003, p = .045) between serum BDNF and HAM-D scores in all patients. In a preliminary examination, reduced BDNF values of three drug-naive patients recovered to basal levels after antidepressant treatment. Our study suggests that low BDNF levels may play a pivotal role in the pathophysiol. of MDD and that antidepressants may increase BDNF in depressed patients.

CC 1-11 (Pharmacology)

Section cross-reference(s): 14

IT Mental disorder

(depression; alterations of brain-derived neurotrophic factor (BDNF) in depressed patients with or without antidepressants)

IT 50-49-7, Imipramine 14028-44-5, Amoxapine 61869-08-7, Paroxetine 92623-85-3, Milnacipran

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(alterations of brain-derived neurotrophic factor (BDNF) in depressed patients with or without antidepressants)

REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 231 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2003:231841 HCAPLUS
DOCUMENT NUMBER: 139:159805
TITLE: Regulation of GRK 2 and 6, β -arrestin-2 and associated proteins in the prefrontal cortex of drug-free and antidepressant drug-treated subjects with major depression
AUTHOR(S): Grange-Midroit, Muriel; Garcia-Sevilla, Jesus A.; Ferrer-Alcon, Marcel; La Harpe, Romano; Huguelet, Philippe; Guimon, Jose
CORPORATE SOURCE: H.U.G., Department of Psychiatry, Clinical Research Unit, University of Geneva, Geneva, Chene-Bourg, Belle-Idee (Les Voirons), CH-1225, Switz.
SOURCE: Molecular Brain Research (2003), 111(1-2), 31-41
CODEN: MBREE4; ISSN: 0169-328X
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB G protein-coupled receptor kinases (GRKs) and β -arrestin-2 play a crucial role in the regulation of neurotransmitter receptors in brain. In this study, GRK 2, GRK 6, β -arrestin-2 and associated proteins (G β proteins and protein phosphatase (PP)-2A) were quantitated in parallel (immunodensity with specific antibodies) in brains of depressed subjects (drug-free and antidepressant-treated) to investigate the effect of major depression and antidepressant drugs on these receptor regulatory proteins. Specimens of the prefrontal cortex (Brodmann's area 9) were collected from 19 suicide and non-suicide depressed subjects and 13 control subjects. In drug-free (n=9), but not in antidepressant-treated (n=10), depressed subjects an increase in the d. of membrane-associated GRK 2 (30%, n=9, P=0.005) was found compared with that in sex-, age-, and PMD-matched controls. Comparison between drug-free and antidepressant-treated depressed subjects showed that GRK 2 was reduced in membrane (39%, n=10, P=0.008) and cytosolic (44%, n=10, P=0.09) prepns. after antidepressant drug treatment. In contrast, membrane-associated GRK 6 (drug-free and antidepressant-treated depressed subjects) was found unchanged when compared with that in matched controls. Similarly, the densities of β -arrestin-2, PP-2A, and G β proteins were not significantly different from those in matched controls. There was a pos. correlation between the immunodensities of GRK 2 and β -arrestin-2 in membrane prepns. (r=0.48, n=19, P=0.04), suggesting that both proteins are regulated in a coordinated manner in brains of depressed subjects. The results of this study indicate that major depression is associated with upregulation of brain GRK 2, but not GRK 6, and that antidepressant drug treatment appears to induce downregulation of GRK 2 protein.
CC 1-11 (Pharmacology)
Section cross-reference(s): 2, 6, 7
IT **Mental disorder**
(major **depression**; regulation of GRK 2 and 6, β -arrestin-2 and associated proteins in prefrontal cortex of drug-free and antidepressant-treated subjects with major **depression**)
IT 50-47-5, Desipramine 52-53-9, Verapamil 72-69-5, Nortriptyline 303-49-1, Clomipramine 739-71-9, Trimipramine 2058-52-8, Clotiapine 19794-93-5, Trazodone 59729-33-8, Citalopram 93413-69-5, Venlafaxine
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(regulation of GRK 2 and 6, β -arrestin-2 and associated proteins in prefrontal cortex of drug-free and antidepressant-treated subjects with major **depression**)

REFERENCE COUNT: 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 232 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN
 ACCESSION NUMBER: 2003:119911 HCAPLUS
 DOCUMENT NUMBER: 138:198059
 TITLE: Duloxetine: An antidepressant that inhibits both
 norepinephrine and serotonin uptake
 AUTHOR(S): Kirwin, Jennifer L.; Goren, Jessica L.
 CORPORATE SOURCE: Department of Pharmacy Practice, Northeastern
 University, Boston, MA, USA
 SOURCE: Formulary (2003), 38(1), 29-30, 33-37
 CODEN: FORMF9; ISSN: 1082-801X
 PUBLISHER: Advanstar Communications, Inc.
 DOCUMENT TYPE: Journal; General Review
 LANGUAGE: English
 AB A review. Depression is a leading cause of morbidity and mortality in the
 United States, costing billions of dollars per yr in direct and indirect
 medical costs and losses in productivity. Patients with major depressive
 disorder (MDD) may experience both psychol. and medical complaints,
 including somatic sensations or pain. Many antidepressants are available
 in the United States to treat depression, but only 50% to 60% of patients
 respond to initial antidepressant treatment. Currently available
 treatments are limited by delayed onset of antidepressant effects and
 treatment resistance. Duloxetine is a re-uptake inhibitor at serotonergic
 and noradrenergic neurons and appears to have low affinity for other
 neurotransmitter systems. In three published clin. trials in patients
 with MDD, duloxetine was well tolerated and more effective than placebo.
 Further study is needed to compare its efficacy with that of other
 antidepressants, to prospectively assess time to onset of antidepressant
 effect, and to clarify effects on somatic symptoms and potential adverse
 cardiovascular and sexual effects. Duloxetine is also under investigation
 for the treatment of stress urinary incontinence in women. Preliminary
 information suggests that duloxetine therapy reduces the number of
 incontinence episodes. Duloxetine has been deemed "approvable" for the
 treatment of MDD and will be Co-marketed under the trade name Cymbalta by
 Eli Lilly and Company and Boehringer Ingelheim.
 CC 1-0 (Pharmacology)
 IT **Mental disorder**
 (major **depression**; antidepressant duloxetine inhibits both
 norepinephrine and serotonin uptake in treatment of major depressive
 disorder patients)
 IT **116539-59-4, Duloxetine**
 RL: ADV (Adverse effect, including toxicity); **DMA (Drug mechanism of**
action); **PAC (Pharmacological activity)**; **PKT**
(Pharmacokinetics); **THU (Therapeutic use)**; BIOL (Biological
 study); USES (Uses)
 (antidepressant duloxetine inhibits both norepinephrine and serotonin
 uptake in treatment of major **depressive** disorder patients)
 REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS
 RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 233 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN
 ACCESSION NUMBER: 2003:668889 HCAPLUS
 DOCUMENT NUMBER: 139:270911
 TITLE: New treatment of depression in Parkinson's disease
 AUTHOR(S): Maruyama, Tetsuhiro
 CORPORATE SOURCE: Iida Municipal Hospital, Japan
 SOURCE: International Journal of Psychiatry in Clinical

Practice (2003), 7(Suppl. 1), 25-27
CODEN: IJPCFZ; ISSN: 1365-1501
PUBLISHER: Taylor & Francis
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The serotonin and noradrenaline reuptake inhibitor milnacipran effectively improved the specific depressive symptoms associated with Parkinson's disease, including apathy and anhedonia.
CC 1-11 (Pharmacology)
IT **Mental disorder**
(**depression**; **depression** in Parkinson's disease treatment by serotonin/noradrenaline reuptake inhibitor milnacipran)
IT 92623-85-3, Milnacipran
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**depression** in Parkinson's disease treatment by serotonin/noradrenaline reuptake inhibitor milnacipran)
REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 234 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:136788 HCAPLUS
DOCUMENT NUMBER: 138:296948
TITLE: Achieving remission from depression with venlafaxine and venlafaxine extended release: A literature review of comparative studies with selective serotonin reuptake inhibitors
AUTHOR(S): Rudolph, R. L.
CORPORATE SOURCE: Cyberonics, Houston, TX, 77058, USA
SOURCE: Acta Psychiatrica Scandinavica, Supplementum (2003), 415, 24-30
CODEN: ASSUA6; ISSN: 0065-1591
PUBLISHER: Blackwell Munksgaard
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. Objective: To evaluate data supporting the ability of venlafaxine, an antidepressant with a dual mechanism of action, to produce remission from depression. Method: Review of multicenter, double-blind, randomized studies comparing venlafaxine or venlafaxine extended release (XR) with a selective serotonin reuptake inhibitor (SSRI), using Hamilton Depression Rating Scale total scores in the range of ≤ 7 and < 10 as the final outcome measure, to evaluate the ability of venlafaxine/venlafaxine XR to produce full remission from depression. Venlafaxine/venlafaxine XR demonstrated higher rates of remission than did the SSRIs and placebo. With full remission rather than response as the measure of outcome, venlafaxine/venlafaxine XR demonstrated more robust antidepressant efficacy than the SSRIs and placebo. This finding suggests that venlafaxine/venlafaxine XR are appropriate standard-of-care therapies for the treatment of patients with major depressive disorder.
CC 1-0 (Pharmacology)
IT **Mental disorder**
(major **depression**; achieving remission from **depression** with venlafaxine and venlafaxine extended release vs. selective serotonin reuptake inhibitors for patients with major **depression**)
IT 93413-69-5, Venlafaxine
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(achieving remission from **depression** with venlafaxine and

venlafaxine extended release vs. selective serotonin reuptake
inhibitors for patients with major depression)

REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 235 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2003:64048 HCAPLUS

DOCUMENT NUMBER: 139:240121

TITLE: Single-blind Comparison of Venlafaxine and
Nortriptyline in Elderly Major Depression

AUTHOR(S): Gasto, Cristobal; Navarro, Victor; Marcos, Teodoro;
Portella, Maria J.; Torra, Merce; Rodamilans, Miquel
CORPORATE SOURCE: Clinical Institute of Phycology and Toxicology Unit,
Hospital Clinic, University of Barcelona, Barcelona,
Spain

SOURCE: Journal of Clinical Psychopharmacology (2003), 23(1),
21-26

CODEN: JCPYDR; ISSN: 0271-0749

PUBLISHER: Lippincott Williams & Wilkins

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The objective of this single-blind study was to compare the efficacy and
safety of venlafaxine extended-release and nortriptyline in elderly
patients with moderate to severe major depression. In- and out-patients
(N=68) with unipolar major depression were randomized to receive 6-mo
treatment with either nortriptyline or venlafaxine. Outcomes of the two
groups were compared using measures including the Hamilton Depression
Rating Scale (HDRS) and the Newcastle Scale. Side effects were assessed
with the UKU side-effect rating scale. Of the 34 venlafaxine-treated
patients, 22 were remitters, 7 were nonremitters, and 5 dropped out. The
intent-to-treat remission rate was 71% (22 of 31). Of the 34 who received
nortriptyline, 21 were remitters, 7 were nonremitters, and 6 dropped out.
The intent-to-treat remission rate was 70% (21 of 30). These results
suggest that the remission rate with a therapeutic plasma level of
nortriptyline is similar to the remission rate with a standard dose of
venlafaxine in this group of elderly major depressed patients. No
significant differences were observed between dropout rates in the two
groups, but autonomic side-effects were significantly more frequent for
nortriptyline than for venlafaxine. These results confirm the efficacy
and safety of venlafaxine extended-release for treating elderly major
depression.

CC 1-11 (Pharmacology)

Section cross-reference(s): 63

IT **Mental disorder**

(major **depression**; single-blind comparison of venlafaxine and
nortriptyline in elderly major **depression**)

IT 72-69-5, Nortriptyline 93413-69-5, Venlafaxine

RL: ADV (Adverse effect, including toxicity); PKT

(Pharmacokinetics); THU (Therapeutic use); BIOL (Biological
study); USES (Uses)

(single-blind comparison of venlafaxine and nortriptyline in elderly
major **depression**)

REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 236 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2002:290820 HCAPLUS

DOCUMENT NUMBER: 136:304102

TITLE: (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane,

compositions thereof, and uses as an anti-depressant agent

INVENTOR(S): Lippa, Arnold Stan; Epstein, Joseph William
 PATENT ASSIGNEE(S): Dov Pharmaceutical, Inc., USA
 SOURCE: U.S., 7 pp.
 CODEN: USXXAM

DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6372919	B1	20020416	US 2001-758883	20010111
CA 2434616	AA	20020829	CA 2002-2434616	20020111
WO 2002066427	A2	20020829	WO 2002-US845	20020111
WO 2002066427	A3	20030313		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
EP 1349835	A2	20031008	EP 2002-720783	20020111
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
BR 2002006434	A	20031230	BR 2002-6434	20020111
CN 1496349	A	20040512	CN 2002-806351	20020111
ZA 2003005440	A	20040715	ZA 2003-5440	20020111
JP 2005500983	T2	20050113	JP 2002-565944	20020111
NZ 527101	A	20050826	NZ 2002-527101	20020111
NO 2003003165	A	20030904	NO 2003-3165	20030710
US 2004132797	A1	20040708	US 2004-466457	20040210
PRIORITY APPLN. INFO.:			US 2001-758883	A 20010111
			WO 2002-US845	W 20020111

AB The present invention relates to (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane and pharmaceutically acceptable salts thereof, compns. comprising (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane or a pharmaceutically acceptable salt thereof, and methods for treating or preventing depression in a patient comprising administering (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane or a pharmaceutically acceptable salt thereof. The (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane or pharmaceutically acceptable salt thereof is preferably substantially free of its corresponding (-)-enantiomer. The + isomer is obtained by HPLC resolution on a CHIRALPAK AD column. The + isomer has greater affinity for both norepinephrine and serotonin uptake sites in rat forebrain membranes than the ± compound. The + isomer is administered along with a known antidepressant, anxiolytic, antipsychotic or antiobesity agent in treatment of various depression conditions including depression associated with anxiety, seizures, menopause, alcoholism, etc.

IC ICM C07D209-52
 ICS A61K031-403

INCL 548452000

CC 1-11 (Pharmacology)

IT **Mental disorder**

(affective, seasonal, **depression** associated with;
(+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane in combination
with other agents for treatment of **depression**)

IT **Mental disorder**
(bipolar disorder; (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane
in combination with other agents for treatment of **depression**)

IT **Mental disorder**
(**depression**; (+)-1-(3,4-dichlorophenyl)-3-
azabicyclo[3.1.0]hexane in combination with other agents for treatment
of **depression**)

IT **Mental disorder**
(neurotic **depression**; (+)-1-(3,4-dichlorophenyl)-3-
azabicyclo[3.1.0]hexane in combination with other agents for treatment
of **depression**)

IT **Mental disorder**
(unipolar **depression**; (+)-1-(3,4-dichlorophenyl)-3-
azabicyclo[3.1.0]hexane in combination with other agents for treatment
of **depression**)

IT 50-47-5, Desipramine 50-48-6, Amitriptyline 50-49-7, Imipramine
50-52-2, Thioridazine 50-53-3, Chlorpromazine, biological studies
51-64-9, Dextroamphetamine 51-71-8, Phenelzine 52-86-8, Haloperidol
58-25-3, Chlordiazepoxide 58-39-9, Perphenazine 69-23-8, Fluphenazine
72-69-5, Nortriptyline 90-84-6, Diethylpropion 113-59-7,
Chlorprothixene 117-89-5, Trifluoperazine 122-09-8, Phentermine
134-49-6, Phenmetrazine 155-09-9, Tranlycypromine 156-08-1,
Benzphetamine 300-62-9, Amphetamine 303-49-1, Clomipramine 438-60-8,
Protriptyline 439-14-5, Diazepam 458-24-2, Fenfluramine 537-46-2,
Methamphetamine 604-75-1, Oxazepam 634-03-7, Phendimetrazine
739-71-9, Trimipramine 846-49-1, Lorazepam 1622-61-3, Clonazepam
1668-19-5, Doxepine 1977-10-2, Loxapine 2062-78-4, Pimozide
2955-38-6, Prazepam 3239-44-9, Dexfenfluramine 3313-26-6, Thiothixene
5714-00-1, Acetophenazine maleate 5786-21-0, Clozapine 7416-34-4,
Molindone 10262-69-8, Maprotiline 14028-44-5, Amoxapine 14611-51-9,
Selegiline 14838-15-4, Phenylpropanolamine 19794-93-5, Trazodone
22232-71-9, Mazindol 23092-17-3, Halazepam 23887-31-2, Clorazepate
28981-97-7, Alprazolam 32672-69-8, Mesoridazine besylate 34911-55-2,
Bupropion 36505-84-7, Buspirone 54739-18-3, Fluvoxamine 54910-89-3,
Fluoxetine 61869-08-7, Paroxetine 79617-96-2, Sertraline 83366-66-9,
Nefazodone 93413-69-5, Venlafaxine 106266-06-2, Risperidone
106650-56-0, Sibutramine

RL: **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
((+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane in combination
with other agents for treatment of **depression**)

REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 237 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2002:797248 HCAPLUS

DOCUMENT NUMBER: 139:29926

TITLE: Major depressive episodes and diet pills

AUTHOR(S): Patten, Scott B.

CORPORATE SOURCE: Departments of Community Health Sciences and
Psychiatry, University of Calgary, Calgary, AB, T2N
4N1, Can.

SOURCE: Expert Opinion on Pharmacotherapy (2002), 3(10),
1405-1409

CODEN: EOPHF7; ISSN: 1465-6566

PUBLISHER: Ashley Publications Ltd.

DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

AB A review. A variety of medications used to assist with weight loss have been implicated in the precipitation or induction of depressive symptoms and disorders.

This is true of a large number of phenylethylamine agents possessing psychostimulant properties, non-phenylethylamine psychostimulants (e.g., caffeine) and the serotonergic agent, fenfluramine. There is, as yet, no substantial evidence linking the more modern weight loss drugs, sibutramine and orlistat, to the etiol. of major depression. Nevertheless, when these drugs are used, major depression will continue to be an important clin. consideration because of the elevated frequency with which major depression occurs in obese patients, the contribution that major depression may make to poor outcomes in non-pharmacol. weight loss treatment and because of the interplay between symptoms of depression and weight loss treatment.

CC 1-0 (Pharmacology)

IT **Mental disorder**

(major **depression**; major depressive episodes and diet pills)

IT 58-08-2, Caffeine, biological studies 64-04-0, Benzeneethanamine
458-24-2, Fenfluramine 96829-58-2, Orlistat **106650-56-0**,
Sibutramine

RL: ADV (Adverse effect, including toxicity); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)

(major **depressive** episodes and diet pills)

REFERENCE COUNT: 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 238 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2002:973159 HCAPLUS

DOCUMENT NUMBER: 138:198489

TITLE: Association study of angiotensin I-converting enzyme
polymorphism and symptomatology and antidepressant
response in major depressive disorders

AUTHOR(S): Hong, C.-J.; Wang, Y.-C.; Tsai, S.-J.

CORPORATE SOURCE: Department of Psychiatry, Veterans General
Hospital-Taipei, Taipei, Peop. Rep. China

SOURCE: Journal of Neural Transmission (2002), 109(9),
1209-1214

CODEN: JNTRF3; ISSN: 1435-1463

PUBLISHER: Springer-Verlag Wien

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Angiotensin-converting enzyme (ACE) inhibitor has mood-elevating effects, and central ACE activity is increased for suicidal patients. In addition, substance P (SP), which is degraded by ACE, has been implicated in the pathogenesis of, and evaluated in the treatment for, major depressive disorder (MDD). The present study has tested the hypothesis that an ACE-gene insertion/deletion (I/D) polymorphism is associated with onset age, clin. manifestations, suicide history, and/or antidepressant response for two groups of MDD patients. No significant differences were demonstrated for onset age ($p = 0.520$), suicide history ($p = 0.823$), or baseline, total and cluster scores for Hamilton Depression Rating Scale comparing the three ACE genotypes. Further, previous findings that this ACE polymorphism is associated with therapeutic antidepressant effects were not replicated. The results demonstrate that these ACE variants did not play a major role in the clin. manifestations or antidepressant response for our MDD patients.

CC 1-11 (Pharmacology)

Section cross-reference(s): 3, 14

IT **Mental disorder**
(major depression; ACE polymorphism, phenotype and antidepressant response in major depressive disorders)
IT 54910-89-3, Fluoxetine 93413-69-5, Venlafaxine
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(ACE polymorphism, phenotype and antidepressant response in major depressive disorders)
REFERENCE COUNT: 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 239 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:680942 HCAPLUS
DOCUMENT NUMBER: 137:210862
TITLE: Efficacy of venlafaxine in patients with major depressive disorder who have unsustained or no response to selective serotonin reuptake inhibitors: an open-label, uncontrolled study
AUTHOR(S): Kaplan, Eric Michael
CORPORATE SOURCE: University of South Florida, Tampa, FL, USA
SOURCE: Clinical Therapeutics (2002), 24(7), 1194-1200
CODEN: CLTHDG; ISSN: 0149-2918
PUBLISHER: Excerpta Medica, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Approx. half of patients who are prescribed selective serotonin re-uptake inhibitors (SSRIs) either do not respond to treatment or do not experience a sustained response. The purpose of this study was to assess the efficacy of venlafaxine immediate-release (IR) and extended-release (XR) in outpatients who either did not respond to SSRI treatment or did not maintain a sustained response. Outpatients who met the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria for major depressive disorder who were previously treated with an SSRI (fluoxetine ≥ 20 mg/d; sertraline ≥ 50 mg/d; paroxetine ≥ 20 mg/d) for ≥ 6 wk, but demonstrated an inadequate or unsustained response, were switched to venlafaxine (IR or XR formulation, 50-400 mg/d, titrated from 37.5 mg/d) for ≥ 6 wk. Response at 6 to 8 wk was defined as total score ≤ 10 on the modified 25-item Hamilton Depression (HAM-D25) rating scale or total score ≥ 5 on the 21-item Patient Global Improvement (PGI-21) scale. Remission was defined as a HAM-D25 total score ≤ 8 or PGI-21 score ≥ 7 . Tests were administered by an unblinded, board-certified psychiatrist. A total of 73 patients (54 women, 19 men; mean age, 38.6 yr) were enrolled and treated with venlafaxine IR (n = 63) or venlafaxine XR (n = 10); 33 were SSRI nonresponders and 36 had an unsustained response to SSRI treatment. Four patients receiving venlafaxine IR discontinued due to drug-related adverse events (agitation, sedation, or nausea). Data from these patients were excluded from the anal. After 6 to 8 wk of treatment, 94.2% (65/69) of patients were considered responders (HAM-D25 or PGI-21 criteria); 91.3% (63/69) of patients responded to treatment as assessed by both measures. Eighty-seven percent (60/69) and 85.5% (59/69) of patients achieved remission based on HAM-D25 and PGI-21 criteria, resp. Response/remission rates were comparable among patients treated with SSRIs, regardless of whether patients had failed to respond to treatment with 1 or 2 SSRIs. Venlafaxine IR/venlafaxine XR may be effective in outpatients with major depressive disorder who do not respond or have an unsustained response to SSRIs. However, randomized, controlled trials are needed before any conclusions can be drawn about the efficacy of this agent in this population.

CC 1-11 (Pharmacology)
 IT **Mental disorder**
 (major **depression**; efficacy of venlafaxine in patients with major depressive disorder who have unsustained or no response to selective serotonin reuptake inhibitors)
 IT **93413-69-5, Venlafaxine**
 RL: ADV (Adverse effect, including toxicity); **PAC (Pharmacological activity)**; **THU (Therapeutic use)**; BIOL (Biological study);
 USES (Uses)
 (efficacy of venlafaxine in patients with major **depressive** disorder who have unsustained or no response to selective serotonin reuptake inhibitors)
 REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 240 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN
 ACCESSION NUMBER: 2002:950980 HCAPLUS
 DOCUMENT NUMBER: 139:143734
 TITLE: Comparative efficacy between venlafaxine and SSRIs: a pooled analysis of patients with depression
 AUTHOR(S): Stahl, Stephen M.; Entsuah, Richard; Rudolph, Richard L.
 CORPORATE SOURCE: The Neuroscience Education Institute (SMS), Carlsbad, CA, USA
 SOURCE: Biological Psychiatry (2002), 52(12), 1166-1174
 CODEN: BIPCBF; ISSN: 0006-3223
 PUBLISHER: Elsevier Science Inc.
 DOCUMENT TYPE: Journal
 LANGUAGE: English

AB Serotonergic and adrenergic enhancement may be synergistic and more effective than serotonergic enhancement alone in treating depression. The dual serotonin-norepinephrine reuptake inhibitor (SNRI) venlafaxine is a dual reuptake inhibitor that may therefore offer greater efficacy than selective serotonin reuptake inhibitors (SSRIs). Data from eight randomized, double-blind, controlled studies were pooled to compare efficacy in depressed patients receiving venlafaxine/venlafaxine extended release (XR), SSRIs, or placebo for ≤ 8 wk. The mean changes from baseline in the 21-item Hamilton Rating Scale for Depression (HAM-D21), Montgomery-Asberg Depression Rating Scale (MADRS), and Clin. Global Impressions-Global Improvement (CGI-I) and CGI-Severity of Illness (CGI-S) item scores were compared, as were response rates derived from these scales. Statistically significant differences in mean HAM-D21 score decrease between venlafaxine (14.5) and SSRIs (12.6) and between the active treatments and placebo (11.3) were observed. Venlafaxine significantly decreased the mean MADRS scores more than SSRIs (17.8 vs. 15.9), and both treatments were significantly better than placebo (12.9). The same pattern of significance for CGI-I, HAM-D21, and MADRS response rates between venlafaxine (71%, 64%, and 67%, resp.), SSRIs (64%, 57%, and 59%, resp.), and placebo (50%, 42%, and 41%, resp.) was observed. Thus, venlafaxine was significantly more effective than SSRIs in improving depression, perhaps due to enhancing both serotonin and norepinephrine.

CC 1-11 (Pharmacology)
 IT **Mental disorder**
 (**depression**; comparative efficacy between venlafaxine and SSRIs in a pooled anal. of patients with **depression**)
 IT 54739-18-3, Fluvoxamine 54910-89-3, Fluoxetine 61869-08-7, Paroxetine
93413-69-5, Venlafaxine
 RL: ADV (Adverse effect, including toxicity); **PAC (Pharmacological activity)**; **THU (Therapeutic use)**; BIOL (Biological study);

USES (Uses)

(comparative efficacy between venlafaxine and SSRIs in a pooled anal.
of patients with **depression**)

REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 241 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2002:701995 HCAPLUS

DOCUMENT NUMBER: 138:314347

TITLE: Efficacy of venlafaxine in major depression resistant
to selective serotonin reuptake inhibitors

AUTHOR(S): Saiz-Ruiz, Jeronimo; Ibanez, Angela; Diaz-Marsa,
Marina; Arias, Francisco; Padin, Jesus;
Martin-Carrasco, Manuel; Montes, Jose Manuel;
Ferrando, Laura; Carrasco, Jose Luis;
Martin-Ballesteros, Eloy; Jorda, Lluís; Chamorro,
Lorenzo

CORPORATE SOURCE: Servicio de Psiquiatria, Grupo de Investigacion "Ramon
y Cajal", Universidad de Alcala, Hospital Ramon y
Cajal, Madrid, 28034, Spain

SOURCE: Progress in Neuro-Psychopharmacology & Biological
Psychiatry (2002), 26(6), 1129-1134

CODEN: PNPPD7; ISSN: 0278-5846

PUBLISHER: Elsevier Science Inc.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Introduction: Some studies suggest that venlafaxine, due to its
pharmacodynamic characteristics, could be an effective drug in depression,
resistant to other antidepressive agents. This investigation explores the
efficacy and tolerability of venlafaxine in major depression, resistant to
a selective serotonin reuptake inhibitor (SSRI). Methods: A multicenter
naturalistic study was performed during 6 mo and included those patients
diagnosed of major depression according to the criteria of DSM-IV who had
a min. score of 18 on the Hamilton Depression Rating Scale (HAM-D) and who
had not responded to previous treatment with a SSRI at therapeutic doses
for a min. of 4 wk. The assessment of efficacy was performed with the
HAM-D scale, the Montgomery-Asberg Depression Rating Scale (MADRS), the
Hamilton Anxiety Rating Scale (HAM-A) and the Global Clin. Impression
(GCI). Tolerability was evaluated by recording the adverse reactions and
with the GCI score on overall drug tolerability. Results: A total of 69
patients, of which 59 were evaluable for efficacy (they had fulfilled at
least 4 wk of treatment), were included. About 81% of all of them
obtained a reduction of at least 50% in the HAM-D, 74% were considered as
"quite improved" or "very improved" in the GCI and 69% met both criteria.
The mean dose of venlafaxine used was 170.4 mg. Of the 21 patients who
did not complete the 6 mo of treatment, 3 were due to lack of efficacy, 6
due to adverse effects and 12 for other reasons. About 89.2% of side
effects were considered as mild or moderate. Conclusion: The results of
our study support the efficacy and tolerability of venlafaxine in patients
suffering from depression who have not responded to SSRI treatment.

CC 1-11 (Pharmacology)

IT **Mental disorder**

(**depression**; venlafaxine efficacy in major **depression**
resistant to selective serotonin reuptake inhibitors)

IT 93413-69-5, Venlafaxine

RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological
activity); THU (Therapeutic use); BIOL (Biological study);

USES (Uses)

(venlafaxine efficacy in major **depression** resistant to

selective serotonin reuptake inhibitors)

REFERENCE COUNT: 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 242 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2002:708136 HCAPLUS

DOCUMENT NUMBER: 137:242084

TITLE: Lamotrigine as an augmentation agent in
treatment-resistant depression

AUTHOR(S): Barbee, James G.; Jamhour, Nowal J.

CORPORATE SOURCE: Department of Psychiatry, Louisiana State University
Health Sciences Center, New Orleans, LA, 70122, USA

SOURCE: Journal of Clinical Psychiatry (2002), 63(8), 737-741
CODEN: JCLPDE; ISSN: 0160-6689

PUBLISHER: Physicians Postgraduate Press, Inc.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Background: The anticonvulsant lamotrigine has been reported to be
efficacious and well tolerated as monotherapy in the treatment of bipolar
patients as well as in treatment-refractory bipolar disorder. However,
there is a paucity of research on the use of lamotrigine as an
augmentation agent in treatment-refractory unipolar major depressive
disorder. Method: This study was a retrospective chart review on the
efficacy of lamotrigine augmentation in 37 individuals diagnosed with
chronic or recurrent major depressive disorder (DSM-IV) who had failed to
respond adequately to at least 2 previous trials of antidepressants.
Thirty-one patients who were on lamotrigine treatment for at least 6 wk (6
discontinued prematurely due to adverse events) took a mean dose of 112.90
mg/day for a mean of 41.80 wk. The primary efficacy parameter for this
study was the Clin. Global Impressions scale, which was retrospectively
applied. In addition, these data were supplemented by an anal. of
prospectively rated Global Assessment of Functioning scores. Results: On
the basis of intent-to-treat anal., response rates were as follows: 40.5%
(15/37) much improved or very much improved, 21.6% (8/37) mildly improved,
and 37.8% (14/37) unchanged. The percentage of patients who were rated
much or very much improved and completed 6 wk on the drug was 48.4%
(15/31). No differences were found in the doses of lamotrigine given to
responders and nonresponders. Conclusion: Analyses revealed that
lamotrigine treatment was most effective for patients who had been
depressed for shorter periods of time and had failed fewer previous trials
of antidepressants. Data also suggested a trend toward increased response
for patients with comorbid anxiety disorders and/or chronic pain
syndromes.

CC 1-11 (Pharmacology)

IT **Mental disorder**

(major **depression**; lamotrigine as augmentation agent in
treatment-resistant **depression** in humans)

IT 525-66-6, Propranolol 554-13-2, Lithium carbonate 12794-10-4D,
Benzodiazepine, derivs. 19794-93-5, Trazodone 34911-55-2, Bupropion
36505-84-7, Buspirone 83366-66-9, Nefazodone 85650-52-8, Mirtazapine
93413-69-5, Venlafaxine

RL: PAC (Pharmacological activity); THU (Therapeutic
use); BIOL (Biological study); USES (Uses)

(lamotrigine as augmentation agent in treatment-resistant
depression in humans: concomitant therapy)

REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 243 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2002:314348 HCAPLUS
DOCUMENT NUMBER: 136:380010
TITLE: Venlafaxine versus stimulant therapy in patients with
dual diagnosis ADD and depression
AUTHOR(S): Hornig-Rohan, Mady; Amsterdam, Jay D.
CORPORATE SOURCE: Depression Research Unit, University Science Center,
Philadelphia, PA, 19104, USA
SOURCE: Progress in Neuro-Psychopharmacology & Biological
Psychiatry (2002), 26(3), 585-589
CODEN: PNPPD7; ISSN: 0278-5846
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Adult attention-deficit disorder (ADD) may either present as chronic depression or be comorbid with major depressive disorder (MDD). The present study examined treatment outcome with antidepressants and/or stimulants in adults with ADD who initially presented with a diagnosis of MDD. Seventeen patients with comorbid MDD and ADD were identified: 65% had a history of hyperactivity in childhood, and 41% had a history of treatment nonresponse to two or more antidepressants. Retrospective anal. was performed with patients who received one of three treatments: (i) venlafaxine, bupropion, or tricyclic antidepressant (TCA) monotherapy; (ii) stimulant monotherapy; or (iii) stimulant plus antidepressant therapy. Outcome was based upon change in both MDD and ADD symptoms. Venlafaxine-treated patients (80%) vs. patients taking stimulant therapy alone (33%) had at least a moderate reduction in both MDD and ADD symptoms ($X^2=2.40$, Fisher exact $P=.13$). Similarly, 88% of patients on stimulants plus antidepressant therapy also showed a reduction in both MDD and ADD symptoms (vs. stimulant monotherapy) ($X^2=7.22$, Fisher exact $P=.018$). There was no difference in response rates between venlafaxine monotherapy and combination stimulant plus antidepressant therapy ($X^2=0.13$, Fisher exact $p=ns$). Although preliminary in nature, these data suggest that venlafaxine monotherapy may have similar efficacy to a treatment with a combination of stimulant plus antidepressant therapy, and superior to stimulant therapy alone, in patients with comorbid MDD and ADD. Controlled, prospective trials with larger patient samples will be needed to confirm these preliminary observations.

CC 1-11 (Pharmacology)

IT **Mental disorder**

(attention deficit disorder; venlafaxine vs. stimulant therapy in patients with ADD and **depression**)

IT **Mental disorder**

(major **depression**; venlafaxine vs. stimulant therapy in patients with ADD and **depression**)

IT 50-49-7, Imipramine 51-64-9, Dextroamphetamine 113-45-1, Methylphenidate 7439-93-2, Lithium, biological studies 34911-55-2, Bupropion 61869-08-7, Paroxetine 93413-69-5, Venlafaxine
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study);
USES (Uses)

(venlafaxine vs. stimulant therapy in patients with ADD and **depression**)

REFERENCE COUNT: 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 244 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2002:744786 HCAPLUS

DOCUMENT NUMBER: 137:273108

TITLE: An eight-week, open-label, uncontrolled, multicenter,

phase IV study of remission rates in outpatients and inpatients with major depression treated with venlafaxine

AUTHOR(S) :

Dierick, Michel; De Nayer, Andre; Ansseau, Marc; D'Haenen, Hugo; Cosyns, Paul; Verbruggen, Ward; Seghers, Arlette; Pelc, Isidore; Fossion, Pierre; Stefos, Grigori; Peuskens, Joseph; Malfroid, Michel; Leyman, Sophie; Mignon, Annick

CORPORATE SOURCE:

Neuro-Psychiatrische Kliniek Sint Camillus, Ghent, Belg.

SOURCE:

Current Therapeutic Research (2002), 63(8), 475-485
CODEN: CTCEA9; ISSN: 0011-393X

PUBLISHER:

Excerpta Medica, Inc.

DOCUMENT TYPE:

Journal

LANGUAGE:

English

AB Venlafaxine is a structurally novel antidepressant that is believed to potentiate monoamine activity in the central nervous system. In pre-clin. studies, venlafaxine was shown to inhibit the neuronal uptake of serotonin and norepinephrine and, to a lesser degree, dopamine reuptake, but was without effect on monoamine oxidase (MAO) activity. Clin. trial results from .apprx.3000 patients suggest that venlafaxine is a safe and effective antidepressant with the potential to invoke an early onset of clin. activity. The purpose of this 8-wk, open-label, uncontrolled, multicenter, phase IV study was to examine the extent of remission and symptom relief in outpatients and inpatients with major depressive disorder treated with venlafaxine. This study was conducted at 12 centers across Belgium and Luxembourg. Consecutive, severely depressed inpatients and moderately depressed outpatients aged 18 to 70 yr were eligible. Patients were administered open-label venlafaxine for 8 wk. Dosing was initiated at venlafaxine 75 mg/d (37.5 mg BID), with dose adjustments made throughout the study, to a maximum daily dose of 375 mg for inpatients and 225 mg for outpatients. Results were measured using the Hamilton Depression (HAM-D) scale, the Montgomery-Asberg Depression Rating Scale (MADRS), and the Clin. Global Impression (CGI) scale. A total of 149 consecutive patients (84 females, 65 males; mean age, 46.5 yr; 88 outpatients, 61 inpatients) were enrolled; the intent-to-treat (ITT) population comprised 144 patients (84 outpatients, 60 inpatients); 111 patients (64 outpatients, 47 inpatients) completed the study. At the week 8 visit, 71.3% of patients (77/108) were considered to be responders according to the HAM-D scale; 73.8% (79/107) according to the MADRS; and 78.7% (85/108) according to the CGI scale. A sustained response was achieved in 33.3% of the ITT population (48/144), and at week 8, 50.8% of outpatients (32/63) and 37.8 % of inpatients (17/45) were in remission according to the HAM-D scale. Venlafaxine was well tolerated at all doses, with the most frequently experienced adverse events (AEs) being nausea, sweating, and headache. Fewer inpatients than outpatients reported ≥ 1 AE (57.4% [35/61] and 73.9% [65/88], resp.), despite receiving a higher maximum daily dose of venlafaxine. The results of this study indicate that venlafaxine was a tolerable and effective antidepressant in both outpatients and inpatients, with a significant proportion of patients achieving remission.

CC 1-11 (Pharmacology)

IT **Mental disorder**

(major depression; venlafaxine in patients with major depression)

IT 93413-69-5, Venlafaxine

RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(venlafaxine in patients with major depression)

REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 245 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2003:59290 HCAPLUS

DOCUMENT NUMBER: 138:117592

TITLE: Venlafaxine: the relationship between dose, plasma
concentration and clinical response in depressive
patients

AUTHOR(S): Charlier, C.; Pinto, E.; Ansseau, M.; Plomteux, G.

CORPORATE SOURCE: Toxicology Laboratory, CHU Sart Tilman, University of
Liege, Liege, Belg.

SOURCE: Journal of Psychopharmacology (London, United Kingdom)
(2002), 16(4), 369-372

CODEN: JOPSEQ; ISSN: 0269-8811

PUBLISHER: Sage Publications Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The relationship between plasma drug level of venlafaxine and daily intake
was studied in 89 major depressive inpatients. In addition, changes over
time in severity were assessed weekly in a subgroup of 22 depressed
patients using the Montgomery and Asberg Depression Rating Scale (MADRS)
and the Clin. Global Impression improvement scale. The results indicate a
moderate correlation between daily doses and plasma concns., together with
a higher relationship between improvement on the MADRS scale and concentration
Moreover, plasma concns. (for venlafaxine and its predominant metabolite,
O-desmethylvenlafaxine) up to 400 µg/l can be considered as effective,
as already suggested in a previous study. No case of venlafaxine
discontinuation occurred during the longitudinal study, and the incidence
of adverse event, as estimated by the Target Emergent Symptoms and
Side-effects scale, was low, suggesting that the drug is well tolerated
for such plasma concns.

CC 1-11 (Pharmacology)

IT **Mental disorder**

(major depression; venlafaxine relationship between dose,
plasma concentration, and clin. response in depressive patients)

IT 93413-69-5, Venlafaxine

RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological
activity); PKT (Pharmacokinetics); THU (Therapeutic
use); BIOL (Biological study); USES (Uses)

(venlafaxine relationship between dose, plasma concentration, and clin.
response in depressive patients)

REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 246 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2002:871303 HCAPLUS

DOCUMENT NUMBER: 137:346003

TITLE: Safety and efficacy of high dose of venlafaxine XL in
treatment resistant major depression

AUTHOR(S): Mbaya, P.

CORPORATE SOURCE: Wythenshawe Hospital, Manchester, M23 9LT, UK

SOURCE: Human Psychopharmacology (2002), 17(7), 335-339

CODEN: HUPSEC; ISSN: 0885-6222

PUBLISHER: John Wiley & Sons Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Aim: The aim of the study was to look at efficacy and the safety profile

of high dose (450-600 mg) venlafaxine XL in five patients with treatment resistant major depressive illness. Methods: Five patients with treatment resistant depression were treated with high dose venlafaxine XL. Efficacy was evaluated using the Montgomery-Asberg depression rating scale (MADRS), the 21-item Hamilton rating scale for depression (HAM-D-21) and the clin. global impressions (CGI) scale. Level of functioning was evaluated by social adaptation self-evaluation scale (SASS). Body weight, supine pulse and blood pressure were recorded. Results: The response rate was based on a 50% decrease in MADRS and HAM-D scores between weeks 1 and 24. There was a more than 50% decrease in MADRS scores in 3 of 5 patients and 4 of 5 patients in HAM-D scores. There was a trend to improvement of SASS scores in three of the study patients and in two of them the mean scores were within the normal range. Supine pulse and blood pressure remained stable in four patients, except in one patient where there was a slight increase although the final reading at week 24 was normal. Weight was relatively stable in all three patients where it was recorded, but in one patient there was a slight increase which may have been due to an atypical neuroleptic the patient was taking at the time. Conclusion: High dose venlafaxine was safe, well tolerated and effective in this small number of severe treatment resistant patients with major depression and it also improved social functioning.

CC 1-11 (Pharmacology)

IT **Mental disorder**

(major **depression**; safety and efficacy of high dose of venlafaxine XL in treatment resistant major **depression** patients)

IT 93413-69-5, Venlafaxine

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(safety and efficacy of high dose of venlafaxine XL in treatment resistant major **depression** patients)

REFERENCE COUNT: 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 247 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2002:374760 HCAPLUS

DOCUMENT NUMBER: 137:27670

TITLE: Somatic symptoms, depression, and antidepressant treatment

AUTHOR(S): Fava, Maurizio

CORPORATE SOURCE: Department of Psychiatry, Massachusetts General Hospital, Boston, MA, 02114, USA

SOURCE: Journal of Clinical Psychiatry (2002), 63(4), 305-307 . CODEN: JCLPDE; ISSN: 0160-6689

PUBLISHER: Physicians Postgraduate Press, Inc.

DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

AB A review of a study by Detke et al. (2002), which examined the effect of a novel dual action antidepressant, called duloxetine, on the painful phys. symptoms from a placebo-controlled study of patients suffering from major depressive disorder (MDD).

CC 1-0 (Pharmacology)

IT **Mental disorder**

(major **depression**; somatic symptoms, **depression**, and antidepressant treatment)

IT 116539-59-4, Duloxetine

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(somatic symptoms, **depression**, and antidepressant treatment)

REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 248 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:817539 HCAPLUS
DOCUMENT NUMBER: 137:304165
TITLE: Novel (atypical) antidepressants
AUTHOR(S): Davanzo, Pablo A.
CORPORATE SOURCE: University of California at Los Angeles, Los Angeles,
CA, USA
SOURCE: Medical Psychiatry (2002), 18(Pharmacotherapy for
Child and Adolescent Psychiatric Disorders (2nd
Edition)), 297-316
CODEN: MEPSEN
PUBLISHER: Marcel Dekker, Inc.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. The selective serotonin-reuptake inhibitors(SSRIs) are now the
drugs of choice for the treatment of juvenile depression. Novel
antidepressants [not chemical related to the tricyclics (TCAs) or the SSRIs]
such as bupropion (Wellbutrin), trazodone (Desyrel), nefazodone (Serzone),
mirtazapine (Remeron), and venlafaxine (Effexor) have been prescribed to
children and adolescents for unlabeled (non-FDA-approved) indications.
Their psychopharmacol. profile and relevant pediatric studies are
summarized in this chapter. Together with these agents, we will also
discuss the adjuvant treatment of depression with thyroid hormones.

CC 1-0 (Pharmacology)

IT **Mental disorder**
(depression; novel (atypical) antidepressants for treatment
of children and adolescents with mood disorder and **depression**
)

IT **Mental disorder**
(major **depression**; novel (atypical) antidepressants for
treatment of children and adolescents with mood disorder and
depression)

IT **Mental disorder**
(mood-affecting; novel (atypical) antidepressants for treatment of
children and adolescents with mood disorder and **depression**)

IT 83366-66-9, Nefazodone 85650-52-8, Mirtazapine 93413-69-5,
Venlafaxine
RL: ADV (Adverse effect, including toxicity); DMA (Drug mechanism of
action); PAC (Pharmacological activity); PKT
(Pharmacokinetics); THU (Therapeutic use); BIOL (Biological
study); USES (Uses)
(novel (atypical) antidepressants for treatment of children and
adolescents with mood disorder and **depression**)

REFERENCE COUNT: 59 THERE ARE 59 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 249 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:310166 HCAPLUS
DOCUMENT NUMBER: 136:380001
TITLE: Duloxetine in the treatment of major depressive
disorder: A double-blind clinical trial
AUTHOR(S): Goldstein, David J.; Mallinckrodt, Craig; Lu, Yili;
Demitrack, Mark A.
CORPORATE SOURCE: Duloxetine Antidepressant Team, Eli Lilly and Company.
Eli Lilly Corporate Center, Indianapolis, USA
SOURCE: Journal of Clinical Psychiatry (2002), 63(3), 225-231

CODEN: JCLPDE; ISSN: 0160-6689

PUBLISHER: Physicians Postgraduate Press, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Duloxetine hydrochloride, a dual reuptake inhibitor of serotonin and norepinephrine, was evaluated for therapeutic efficacy and safety/tolerability in the treatment of major depression. In an 8-wk multicenter, double-blind, placebo-controlled study, 173 patients (aged 18-65 yr) with DSM-IV major depressive disorder were randomly allocated to receive placebo (N = 70), duloxetine (N = 70), or fluoxetine, 20 mg q.d. (N = 33). Duloxetine dose was titrated in the first 3 wk in a forced-titration regimen from 40 mg (20 mg b.i.d.) to 120 mg/day (60 mg b.i.d.). Patients were required to have a Clin. Global Impressions (CGI)-Severity of Illness scale score of at least moderate severity (≥ 4) and a 17-item Hamilton Rating Scale for Depression (HAM-D-17) total score of at least 15. Patients could not have had any current primary DSM-IV Axis I diagnosis other than major depressive disorder, or any anxiety disorder as a primary diagnosis within the past year, excluding specific phobias. The primary efficacy measurement was the HAM-D-17 total score, and secondary measures included the Montgomery-Asberg Depression Rating Scale, CGI-Severity of Illness and CGI-Improvement, and Patient Global Impression of Improvement. Safety was evaluated by recording the occurrence of discontinuation rates and treatment-emergent adverse events and by measurement of vital signs and laboratory analytes. Duloxetine was superior to placebo in change on the HAM-D-17 ($p = .009$). Estimated probabilities of response and remission were 64% and 56%, resp., for duloxetine, compared with 52% and 30% for fluoxetine and 48% and 32% for placebo. Duloxetine was numerically superior to fluoxetine on the primary and most of the secondary outcome measures. In general, duloxetine was well tolerated; 76% of patients achieved the maximum dose, and insomnia and asthenia were the only adverse events reported statistically significantly ($p < .05$) more frequently by duloxetine-treated patients compared with placebo-treated patients. These data indicate that duloxetine is efficacious for the treatment of major depressive disorder and is well tolerated and safe.

CC 1-11 (Pharmacology)

IT **Mental disorder**(major **depression**; duloxetine vs. fluoxetine in treatment of patients with major depressive disorder)IT **116539-59-4, Duloxetine**RL: ADV (Adverse effect, including toxicity); **PAC (Pharmacological activity)**; **THU (Therapeutic use)**; BIOL (Biological study);

USES (Uses)

(duloxetine vs. fluoxetine in treatment of patients with major **depressive disorder**)

REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 250 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2003:88319 HCAPLUS

DOCUMENT NUMBER: 138:147627

TITLE: Body weight, the tumor necrosis factor system, and leptin production during treatment with mirtazapine or venlafaxine

AUTHOR(S): Kraus, T.; Haack, M.; Schuld, A.; Hinze-Selch, D.; Koethe, D.; Pollmaecher, T.

CORPORATE SOURCE: Max Planck Institute of Psychiatry, Munich, Germany

SOURCE: Pharmacopsychiatry (2002), 35(6), 220-225

CODEN: PHRMEZ; ISSN: 0176-3679

PUBLISHER: Georg Thieme Verlag
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Weight gain is a frequent and important side effect of psychopharmacotherapy. Recent studies suggest that the fat-cell-derived hormone leptin and the tumor necrosis factor- α (TNF- α) cytokine system are pathophysiol. involved. No information is available concerning the influence of the antidepressants mirtazapine and venlafaxine on these immunoendocrine variables. An open-labeled study was performed in 20 patients suffering from major depression treated with either mirtazapine (N = 11) or venlafaxine (N = 9). During 4 wk, the patients' weight, body mass index (BMI), and plasma levels of leptin, TNF- α , sTNF-R p55, and sTNF-R p75 were assessed. Mirtazapine induced a significant increase in weight (mean weight gain: 2.4 kg) that was evident after the first week of treatment. In parallel, the plasma levels of TNF- α and both soluble TNF receptors increased. In addition, a slight rise in leptin levels, which occurred slowly and was significant only at the end of the 4th week of treatment, was observed. Weight decreased slightly but significantly in patients

treated with venlafaxine (mean weight loss: 0.4 kg), whereas plasma levels of leptin, TNF- α , or soluble TNF receptors did not change significantly. The present results further support the notion that the activation of the TNF- α cytokine system is an early, sensitive, and specific marker of weight gain induced by psychotropic agents. In contrast, the effects of such drugs on leptin production seem to be less sensitive with respect to weight gain and more variable.

CC 1-11 (Pharmacology)

IT **Mental disorder**

(major **depression**; mirtazapine and venlafaxine effect on body weight, tumor necrosis factor system, and leptin production for treatment of major **depression** patients)

IT 85650-52-8, Mirtazapine 93413-69-5, Venlafaxine

RL: **PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)**

(mirtazapine and venlafaxine effect on body weight, tumor necrosis factor system, and leptin production for treatment of major **depression** patients)

REFERENCE COUNT: 51 THERE ARE 51 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 251 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2002:460924 HCAPLUS

DOCUMENT NUMBER: 137:57466

TITLE: Efficacy and safety of venlafaxine-ECT combination in treatment-resistant depression

AUTHOR(S): Gonzalez-Pinto, Ana; Gutierrez, Miguel; Gonzalez, Nekane; Elizagarate, Edorta; Perez De Heredia, Jose L.; Mico, Juan A.

CORPORATE SOURCE: Department of Psychiatry, Hospital Santiago Apostol, Vitoria, Spain

SOURCE: Journal of Neuropsychiatry and Clinical Neurosciences (2002), 14(2), 206-209
CODEN: JNCNE7; ISSN: 0895-0172

PUBLISHER: American Psychiatric Publishing, Inc.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Thirteen patients with treatment-resistant major depression were given venlafaxine, at doses ranging from 150 mg to 375 mg, combined with ECT.

Propofol was used as an anesthetic. Ten of 13 (76.9%) were considered responsive to combined ECT-venlafaxine treatment, and pos. responses were not associated with venlafaxine doses. An asystole episode was observed in 4 patients; these patients had received significantly higher doses of venlafaxine ($P < 0.01$). Treatment seems to be safe at venlafaxine doses < 300 mg/day. At higher doses, with propofol used as anesthetic, the possibility of asystole cannot be ruled out. A possible additive effect of high-dose venlafaxine and propofol-blocking sodium channels are discussed.

CC 1-11 (Pharmacology)

IT **Mental disorder**

(bipolar disorder; venlafaxine-ECT combination in treatment-resistant depression)

IT **Mental disorder**

(major depression; venlafaxine-ECT combination in treatment-resistant depression)

IT **93413-69-5, Venlafaxine**

RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study);

USES (Uses)

(venlafaxine-ECT combination in treatment-resistant depression)

REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 252 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2002:537774 HCAPLUS

DOCUMENT NUMBER: 137:103812

TITLE: Remarkable effect of milnacipran in the treatment of Japanese major depressive patients

AUTHOR(S): Higuchi, Hisashi; Yoshida, Keizo; Takahashi, Hitoshi; Naito, Shingo; Tsukamoto, Kei; Kamata, Mitsuhiro; Ito, Kenichi; Sato, Kazuhiro; Shimizu, Tetsuo

CORPORATE SOURCE: Omagari City Hosp., Omagari, Akita, 014-0067, Japan

SOURCE: Human Psychopharmacology (2002), 17(4), 195-196

CODEN: HUPSEC; ISSN: 0885-6222

PUBLISHER: John Wiley & Sons Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Milnacipran is a new specific serotonin and noradrenaline reuptake inhibitor (SNRI) that has been shown to be equally as effective as tricyclic antidepressants (TCA) in the treatment of depression. We first investigated the antidepressant effect of milnacipran in Japanese patients with major depression in a fixed-dose regimen. We also investigated the relationship between the clin. effects and the plasma levels of milnacipran, because there has been no report on the relationship between the antidepressant response and the plasma levels of milnacipran, except for a preliminary report dealing with 17 patients only. The daily dose was 50 mg/day for the first week, and up to 100 mg/day thereafter. Twenty-three patients (74 %) were responders according to the definition mentioned above. The plasma milnacipran levels of the 31 patients ranged between 44.3 and 156.8 ng/mL. In the present study, no significant correlation was found between the plasma levels of milnacipran and the antidepressant response. However, there are several reports suggesting a significant relationship between plasma levels and the clin. effect of TCAs in endogenous depression or major depression with melancholia. Therefore, it is necessary to investigate the relationship between plasma levels and the antidepressant response of milnacipran in major depressive patients with melancholia in the future.

CC 1-11 (Pharmacology)

IT **Mental disorder**

(major depression; remarkable effect of milnacipran in treatment of major depressive patients)

IT 92623-85-3, Milnacipran

RL: PAC (Pharmacological activity); PKT

(Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(remarkable effect of milnacipran in treatment of major depressive patients)

REFERENCE COUNT:

2

THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 253 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2002:854062 HCAPLUS

DOCUMENT NUMBER: 139:111449

TITLE: Open-Label Evaluation of Venlafaxine Sustained Release in Outpatients with Generalized Anxiety Disorder with Comorbid Major Depression or Dysthymia: Effectiveness, Tolerability and Predictors of Response

AUTHOR(S): Perugi, Giulio; Frare, Franco; Toni, Cristina; Ruffolo, Giuseppe; Torti, Carlo

CORPORATE SOURCE: Department of Psychiatry, Neurobiology, Pharmacology and Biotechnologies, Psychiatry Section, University of Pisa, Institute of Behavioral Sciences G. De Lisio', Carrara, Pisa, Italy

SOURCE: Neuropsychobiology (2002), 46(3), 145-149

CODEN: NPBYAL; ISSN: 0302-282X

PUBLISHER: S. Karger AG

DOCUMENT TYPE: Journal

LANGUAGE: English

AB In a setting of routine clin. practice, 32 outpatients with generalized anxiety disorder (GAD) and major depression (MD) or dysthymia, according to DSM-IV criteria, were consecutively treated with flexible dosages of sustained-release venlafaxine (SR-VF) for at least 8 wk. In a 16-wk follow-up, SR-VF daily dose could be modified on the basis of the therapeutic response and of the side effect profile. Symptomatology modifications were explored by means of the Clin. Global Impression (CGI) scale, Hamilton Rating Scale for Depression (HAM-D), and Hamilton Anxiety Scale (HAM-A). SR-VF was well tolerated and only 2 patients interrupted the treatment before 24 wk; the mean final dose was 135.5 mg (range 75-225); in 26 (81.2%) patients, a statistically significant response was observed in depressive symptomatology within the first 8 wk. The mean total score of HAM-D showed a significant reduction during the first 8 wk of treatment, while the mean total score of HAM-A did not present a significant reduction until week 24. In patients with MD, a statistically significant response was observed after the first 8 wk, while the reduction of the anxiety scores required more time and, in some cases, did not appear at all. Conversely, in patients with GAD and dysthymia, anxious and depressive symptomatology improved simultaneously. Stepwise multiple regression indicated that the improvement of depression is neg. related to a high score of CGI anxiety severity, and the improvement of anxiety is related to the presence of dysthymia and, to a lesser extent, to a short duration of the illness. Our data confirm the effectiveness and tolerability of SR-VF in mixed anxiety-depressive states. The differential response suggests a pathophysiol. and clin. distinction between GAD with comorbid MD or dysthymia.

CC 1-11 (Pharmacology)

IT **Mental disorder**

(**depression**; venlafaxine sustained release efficacy and tolerability in outpatients with generalized anxiety disorder with comorbid major **depression** or dysthymia)

IT **Mental disorder**

(neurotic **depression**; venlafaxine sustained release efficacy and tolerability in outpatients with generalized anxiety disorder with comorbid major **depression** or dysthymia)

IT **93413-69-5, Venlafaxine**

RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(venlafaxine sustained release efficacy and tolerability in outpatients with generalized anxiety disorder with comorbid major **depression** or dysthymia)

REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 254 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2003:743997 HCAPLUS

DOCUMENT NUMBER: 139:301922

TITLE: Venlafaxine compared with fluoxetine in outpatients with depression and concomitant anxiety

AUTHOR(S): De Nayer, Andre; Geerts, Stefaan; Ruelens, Leo; Schittecatte, Michel; De Bleeker, Eugene; Van Eeckhoutte, Ignace; Evrard, Jean-Luc; Linkowski, Paul; Fossion, Pierre; Leyman, Sophie; Mignon, Annick
CORPORATE SOURCE: Hopital Ste Therese, Monlignies sur Sambre, Belg.
SOURCE: International Journal of Neuropsychopharmacology (2002), 5(2), 115-120

CODEN: IJNUFB; ISSN: 1461-1457

PUBLISHER: Cambridge University Press

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The aim of this double-blind study was to compare the efficacy and safety of venlafaxine vs. fluoxetine in the treatment of patients with depression and anxiety. A total of 146 moderately depressed patients with associated anxiety were randomized to receive 75 mg/d venlafaxine or 20 mg/d fluoxetine for 12 wk. Dose increases were permitted after 2 wk of treatment, to 150 mg/d venlafaxine and 40 mg/d fluoxetine, to optimize response. At the final visit, a statistically significantly greater efficacy of venlafaxine over fluoxetine was observed on depressive symptoms and concomitant anxiety, and 75.0 and 50.7% of patients administered venlafaxine and fluoxetine, resp., showed an overall response. A sustained response (for at least 2 wk), present at the end of the study was achieved in 57.8 and 43.3% of patients in the venlafaxine and fluoxetine groups, resp., and at the final visit, 59.4 and 40.3% of patients, resp., were in remission (virtually asymptomatic). Dose increases were required by a greater percentage of patients in the fluoxetine group (52.9%), than in the venlafaxine group (37.1%), and in those patients whose dose was increased, a higher efficacy was again observed with venlafaxine. Venlafaxine and fluoxetine were well tolerated, with the most frequently experienced adverse events being nausea and headache. Fewer patients in the venlafaxine group than in the fluoxetine group reported at least one adverse event (55.7 and 67.1% patients, resp.). Venlafaxine therefore proved to be significantly more effective than fluoxetine in improving depressive symptoms and concomitant anxiety.

CC 1-11 (Pharmacology)

IT **Mental disorder**

(**depression**; venlafaxine vs. fluoxetine in patients with

depression and anxiety)
 IT 54910-89-3, Fluoxetine 93413-69-5, Venlafaxine
 RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study);
 USES (Uses)
 (venlafaxine vs. fluoxetine in patients with depression and anxiety)
 REFERENCE COUNT: 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 255 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN
 ACCESSION NUMBER: 2002:322588 HCAPLUS
 DOCUMENT NUMBER: 136:379400
 TITLE: Common treatment of polycystic ovarian syndrome and major depressive disorder: case report and review
 AUTHOR(S): Rasgon, N. L.; Carter, M. S.; Elman, S.; Bauer, M.; Love, M.; Korenman, S. G.
 CORPORATE SOURCE: Department of Psychiatry and Biobehavioral Sciences and Department of Medicine, Division of Endocrinology, University of California Los Angeles School of Medicine, Los Angeles, CA, USA
 SOURCE: Current Drug Targets: Immune, Endocrine and Metabolic Disorders (2002), 2(1), 97-102
 CODEN: CDTIBT; ISSN: 1568-0088
 PUBLISHER: Bentham Science Publishers Ltd.
 DOCUMENT TYPE: Journal; General Review
 LANGUAGE: English

AB A review. We present the case of a young woman with treatment-resistant major depression, who presented to the Mood Disorders Clinic with a Hamilton Psychiatric Rating Scale for Depression (HAM-D-21) score of 28, after a year-long treatment with Effexor-XR. The patient also had untreated Polycystic Ovarian Syndrome (PCOS). The resolution of her depressive symptoms resulted from the treatment for PCOS with metformin and spironolactone. The patient remained euthymic 5 mo after discontinuation of the antidepressant while continuing therapy for PCOS. We briefly overview of the pertinent literature of the pathophysiol. of PCOS and affective disorders, highlighting an overlap in phenotypical presentations between these two disorders. Dysregulation of the hypothalamo-pituitary axis and various end organ systems are implicated in both PCOS and affective disorders. As such, several clin. and biochem. markers are common to both disorders, namely insulin resistance, obesity, and hyperandrogenism. In addition, these metabolic abnormalities are interrelated, causing women with PCOS or affective disorders to get caught in a "vicious cycle" of hormonal dysregulation. The case report presented here illustrates how treatment of symptoms such as insulin resistance and hyperandrogenism can lead to remission of major depressive disorder and PCOS. We suggest that through treatment of underlying metabolic defects, both the mood of the patient and the metabolic condition of PCOS can be assisted.

CC 1-0 (Pharmacology)

IT **Mental disorder**
 (major depression; treatment of polycystic ovarian syndrome and major depressive disorder)

IT 52-01-7, Spironolactone 657-24-9, Metformin 99300-78-4, Effexor
 RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (treatment of polycystic ovarian syndrome and major depressive disorder)

REFERENCE COUNT: 64 THERE ARE 64 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 256 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN
 ACCESSION NUMBER: 2002:493731 HCAPLUS
 DOCUMENT NUMBER: 137:73155
 TITLE: Noradrenergic antidepressants: does chronic treatment increase or decrease nuclear CREB-P?
 AUTHOR(S): Manier, D. H.; Shelton, R. C.; Sulser, F.
 CORPORATE SOURCE: Department of Psychiatry and Pharmacology, Vanderbilt University Medical Center, Nashville, TN, USA
 SOURCE: Journal of Neural Transmission (2002), 109(1), 91-99
 CODEN: JNTRF3; ISSN: 1435-1463
 PUBLISHER: Springer-Verlag Wien
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 AB Chronic administration of noradrenergic antidepressants causes a desensitization of the beta adrenoceptor coupled adenylate cyclase system. In the present studies, we attempted to answer the question of whether or not this deamplification is reflected beyond the second messenger system. Nuclear CREB-P was determined in frontal cortex of rats following acute and chronic administration of desipramine (DMI) or reboxetine and in human fibroblasts following incubation for 48 h with DMI, reboxetine or venlafaxine. Nuclear CREB-P in the frontal cortex was significantly decreased following chronic administration of DMI or reboxetine. Moreover, incubation of human fibroblasts with DMI or reboxetine, but not with venlafaxine, caused a highly significant reduction in nuclear CREB-P suggesting that the noradrenergic antidepressants exert direct effects beyond beta adrenoceptors. The results are consistent with the view that chronic treatment with antidepressants causes a net deamplification of the norepinephrine mediated signal transduction cascade which might "normalize" the increased noradrenergic activity evident in major depression.
 CC 1-11 (Pharmacology)
 IT **Mental disorder**
 (major **depression**; noradrenergic antidepressants effect on nuclear CREB-P in rat frontal cortex and human fibroblasts: implication for major **depression**)
 IT 50-47-5, Desipramine 71620-89-8, Reboxetine 93413-69-5, Venlafaxine
 RL: **DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study);**
 USES (Uses)
 (noradrenergic antidepressants effect on nuclear CREB-P in rat frontal cortex and human fibroblasts: implication for major **depression**)

REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 257 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN
 ACCESSION NUMBER: 2002:151335 HCAPLUS
 DOCUMENT NUMBER: 137:345885
 TITLE: Does SSRI augmentation with antidepressants that influence noradrenergic function resolve depression in obsessive-compulsive disorder?
 AUTHOR(S): Mancini, Catherine; Van Ameringen, Michael; Farvolden, Peter
 CORPORATE SOURCE: Anxiety Disorders Clinic, McMaster University Medical Centre, Hamilton Health Sciences Corporation,

SOURCE: Hamilton, ON, L8N 3Z5, Can.
Journal of Affective Disorders (2002), 68(1), 59-65
CODEN: JADID7; ISSN: 0165-0327

PUBLISHER: Elsevier Science B.V.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Background: Obsessive compulsive disorder (OCD) often coexists with major depressive disorder (MDD). Serotonergic antidepressant medications have emerged as the treatment of choice for both OCD and MDD. In the usual course of events, both the patient's OCD and depressive symptoms improve in parallel following initiation of serotonin reuptake inhibitor (SRI) treatment for OCD. However, such is not always the case. We report here on a series of ten patients whose OCD but not depression improved following a trial of SRI therapy. Method: Ten patients with OCD and comorbid MDD who experienced a worsening or exacerbation of depressive symptoms while being maintained on an adequate dose of SRI therapy were treated using a combination of SRIs and agents with effects on noradrenergic reuptake. Response to treatment was based on clinician-ratings of severity and improvement of OCD and MDD (CGI-S and CGI-I). Results: Following augmentation, nine of the ten patients had a significant improvement/resolution of their MDD, with little further change in the severity of their OCD. Limitations: Inferences from the results of this study are limited by the lack of a control group, the small sample size, and the use of nonstandardized ratings as measures of symptom severity. Conclusions: These results are of practical significance to clinicians insofar as they suggest a possible guideline to clinicians treating depression in OCD with SSRIs without success.

CC 1-11 (Pharmacology)

IT **Mental disorder**
(major **depression**; selective serotonin reuptake inhibitors (SSRI) augmentation with antidepressants that influence noradrenergic function resolve **depression** in obsessive-compulsive disorder)

IT **Mental disorder**
(obsession-compulsion; selective serotonin reuptake inhibitors (SSRI) augmentation with antidepressants that influence noradrenergic function resolve **depression** in obsessive-compulsive disorder)

IT 50-47-5, Desipramine 72-69-5, Nortriptyline 303-49-1, Clomipramine 1622-61-3, Clonazepam 54739-18-3, Fluvoxamine 61869-08-7, Paroxetine 79617-96-2, Sertraline 93413-69-5, Venlafaxine

RL: **PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)**
(selective serotonin reuptake inhibitors (SSRI) augmentation with antidepressants that influence noradrenergic function resolve **depression** in obsessive-compulsive disorder)

REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 258 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2002:644786 HCAPLUS

DOCUMENT NUMBER: 138:378991

TITLE: A randomised, double-blind comparison of milnacipran and imipramine in the treatment of depression

AUTHOR(S): Van Amerongen, A. P.; Ferrey, G.; Tournoux, A.

CORPORATE SOURCE: Centre Medico-Psychologique Secteur VI, Centre Hospitalier Intercommunal Poissy St-Germain-En-Laye, St-Germain-En-Laye, 78105, Fr.

SOURCE: Journal of Affective Disorders (2002), 72(1), 21-31
CODEN: JADID7; ISSN: 0165-0327

PUBLISHER: Elsevier Science B.V.

DOCUMENT TYPE: Journal
LANGUAGE: English

AB This multicenter, double-blind, randomised trial in 109 patients compared the efficacy and tolerance of the novel selective serotonin and noradrenaline reuptake inhibitor (SNRI) antidepressant milnacipran (50 mg twice daily, n=53) with the established tricyclic agent imipramine (75 mg twice daily, n=56) over a period of 6 wk, in patients with major depression (Montgomery-Asberg depression rating score (MADRS)≥25). Initiation of antidepressant medication was conducted during a 2-wk period of hospitalization, after a 3- to 7-day washout period. Concomitant psychiatric medication was limited to lorazepam, cyamemazine, chloral hydrate and long-term uncomplicated lithium therapy. Assessment for efficacy using the MADRS and Hamilton rating scales of depression, a visual analog scale and global evaluation revealed both agents to be highly effective (P=0.0001) in this group of patients. Milnacipran was found to be of similar efficacy to imipramine. Tolerance, assessed by physiol. and biochem. exams. with routine inventory and spontaneous report of adverse events, revealed a clear advantage for milnacipran. The incidence of anticholinergic events with milnacipran was about half that with imipramine and the overall incidence of adverse events by either reporting method was markedly lower with milnacipran than with imipramine. Furthermore, the patient drop-out rate with imipramine was double that experienced with milnacipran. Milnacipran appears to possess equal antidepressant efficacy to imipramine but with markedly superior tolerance. Therefore, milnacipran constitutes an important new treatment option in major depression.

CC 1-11 (Pharmacology)

IT **Mental disorder**
(major **depression**; randomised, double-blind comparison of milnacipran and imipramine in treatment of **depression**)

IT 50-49-7, Imipramine 92623-85-3, Milnacipran
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study);
USES (Uses)
(randomised, double-blind comparison of milnacipran and imipramine in treatment of **depression**)

REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 259 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2002:740374 HCAPLUS

DOCUMENT NUMBER: 137:257580

TITLE: Achieving remission with venlafaxine and fluoxetine in major depression: its relationship to anxiety symptoms

AUTHOR(S): Davidson, Jonathan R. T.; Meoni, Paolo; Haudiquet, Vincent; Cantillon, Marc; Hackett, David

CORPORATE SOURCE: Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, Durham, NC, USA

SOURCE: Depression and Anxiety (2002), 16(1), 4-13
CODEN: DEANF5; ISSN: 1091-4269

PUBLISHER: Wiley-Liss, Inc.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Venlafaxine, a serotonin and norepinephrine reuptake inhibitor (SNRI), produces significantly higher remission rates in depressed patients than do the selective serotonin reuptake inhibitors (SSRIs). In this anal. of pooled data, we explored the relationship between differences in treatment efficacy, early improvement of symptoms, and severity of baseline anxiety in depressed patients treated with either venlafaxine or fluoxetine. A

pooled anal. was performed on data from 1,454 outpatients with major depression from five double-blind, randomized studies comparing the 6-wk efficacy of venlafaxine (542 patients) with fluoxetine (555 patients). The Hamilton rating scale for depression (HAM-D) total and item scores were analyzed at different treatment times up to 6 wk. Venlafaxine and fluoxetine both produced statistically significant higher response and remission rates compared with placebo starting from week 2 for response and weeks 3 to 4 for remission. Venlafaxine was statistically significantly superior to fluoxetine from week 3 until week 6 in respect of response rate, and from week 2 until week 6 for remission rate. After 1 wk of treatment, greater improvement in individual symptoms was observed in the depressed mood, suicide, and psychic anxiety items of the HAM-D scale for both venlafaxine- and fluoxetine-treated patients compared with placebo. Improvement in psychic anxiety was statistically significantly greater with venlafaxine than with fluoxetine. The presence of baseline psychic anxiety correlated significantly to treatment outcome when analyzing the remission rates. In depressed patients with moderate anxiety (HAM-D psychic anxiety score ≤ 2), venlafaxine statistically significantly increased remission rates compared with placebo from week 4 until week 6, while a significant effect of fluoxetine on remission rates was observed starting at week 6. Remission rates in the severely anxious depressed patients (score > 2) were statistically significantly higher with venlafaxine than placebo starting from week 3 until the end of the study period, but no difference could be observed between fluoxetine and placebo. Baseline severity of psychic anxiety had a significant impact on remission rates after treatment of patients diagnosed with depression. Venlafaxine's superior remission rates in the more severely anxious patients and its ability to improve psychic anxiety as early as week 1 compared with fluoxetine suggest that venlafaxine's early efficacy on anxiety symptoms may be the basis for its superior efficacy in depression.

CC 1-11 (Pharmacology)

IT **Mental disorder**

(major **depression**; achieving remission with venlafaxine and fluoxetine in major **depression** and relationship to anxiety symptoms)

IT 54910-89-3, Fluoxetine 93413-69-5, Venlafaxine

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(achieving remission with venlafaxine and fluoxetine in major **depression** and relationship to anxiety symptoms)

REFERENCE COUNT: 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 260 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2001:434867 HCAPLUS

DOCUMENT NUMBER: 135:29158

TITLE: The combination of a serotonin reuptake inhibitor and irindalone for the treatment of depression and other affective disorders

INVENTOR(S): Bogeso, Klaus Peter; Cremers, Thomas Ivo Franciscus Hubert

PATENT ASSIGNEE(S): H. Lundbeck A/S, Den.

SOURCE: PCT Int. Appl., 29 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001041766	A1	20010614	WO 2000-DK667	20001204
W: AE, AG, AL, AM, AT, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, CZ, DE, DE, DK, DK, DM, DZ, EE, EE, ES, FI, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 2001018508	A5	20010618	AU 2001-18508	20001204
US 2002103249	A1	20020801	US 2000-731411	20001206
TR 200201512	T2	20020923	TR 2002-200201512	20001206
EP 1396267	A2	20040310	EP 2003-27672	20001206
EP 1396267	A3	20040421		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
ZA 2002004391	A	20030901	ZA 2002-4391	20020531
PRIORITY APPLN. INFO.:			US 1999-169245P	P 19991206
			WO 2000-DK667	W 20001204
			EP 2000-981174	A3 20001206
AB	The invention discloses the use of a combination of irindalone and a serotonin reuptake inhibitor, or any other compound which causes an elevation in the level of extracellular serotonin, for the treatment of depression and other affective disorders.			
IC	ICM A61K031-497 ICS A61K031-135; A61K031-137; A61K031-15; A61K031-343; A61K031-4525; A61K031-451; A61K031-496			
CC	1-11 (Pharmacology)			
IT	Mental disorder (affective; irindalone-serotonin reuptake inhibitor combination for treatment of depression and other affective disorders)			
IT	Mental disorder (attention deficit hyperactivity disorder; irindalone-serotonin reuptake inhibitor combination for treatment of depression and other affective disorders)			
IT	Mental disorder (depression , neurotic; irindalone-serotonin reuptake inhibitor combination for treatment of depression and other affective disorders)			
IT	Mental disorder (obsession-compulsion; irindalone-serotonin reuptake inhibitor combination for treatment of depression and other affective disorders)			
IT	Mental disorder (phobia; irindalone-serotonin reuptake inhibitor combination for treatment of depression and other affective disorders)			
IT	Mental disorder (post-traumatic stress disorder; irindalone-serotonin reuptake inhibitor combination for treatment of depression and other affective disorders)			
IT	50-49-7, Imipramine 303-49-1, Clomipramine 54739-18-3, Fluvoxamine 54910-89-3, Fluoxetine 59729-33-8, Citalopram 59859-58-4, Femoxetine 61869-08-7, Paroxetine 79617-96-2, Sertraline 83366-66-9, Nefazodone 93413-69-5, Venlafaxine 96478-43-2, Irindalone 104113-57-7,			

Irindalone tartrate 119356-77-3, Dapoxetine 128196-01-0, Escitalopram
RL: BAC (Biological activity or effector, except adverse); BSU
(Biological study, unclassified); THU (Therapeutic use); BIOL
(Biological study); USES (Uses)

(irindalone-serotonin reuptake inhibitor combination for treatment of
depression and other affective disorders)

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 261 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2001:732456 HCAPLUS

DOCUMENT NUMBER: 136:47860

TITLE: Venlafaxine extended-release: A review of its use in
the management of major depression

AUTHOR(S): Wellington, Keri; Perry, Caroline M.

CORPORATE SOURCE: Adis International Limited, Auckland, N. Z.

SOURCE: CNS Drugs (2001), 15(8), 643-669

CODEN: CNDREF; ISSN: 1172-7047

PUBLISHER: Adis International Ltd.

DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

AB A review. Venlafaxine inhibits presynaptic reuptake of serotonin
(5-hydroxytryptamine; 5-HT) and noradrenaline (norepinephrine).
Venlafaxine extended-release (XR) has been investigated in patients with
major depression and in patients with major depression with associated
anxiety in randomized, double-blind, multicenter trials. A therapeutic
response in patients with major depression was evident at week 2 of
treatment with venlafaxine XR 75 to 225 mg/day in a placebo-controlled
trial. By week 4, the drug was significantly more effective than placebo
at reducing both the Hamilton Rating Scale for Depression (HAM-D) and
Montgomery-Asberg Depression Rating Scale (MADRS) total scores.
Furthermore, cumulative relapse rates were lower among recipients of
venlafaxine XR 75 to 225 mg/day than placebo recipients after 3 and 6 mo
in another trial. Venlafaxine XR 75 to 150 mg/day was significantly more
effective than venlafaxine immediate-release (IR) 75 to 150 mg/day or
placebo during a 12-wk study. Redns. from baseline in all 4 efficacy
parameters (HAM-D, MADRS, HAM-D depressed mood item and the Clin. Global
Impression Severity of Illness scale) were significantly higher among
patients treated with venlafaxine XR than venlafaxine IR or placebo at
week 12 (using an intent-to-treat, last observation carried forward
anal.). Venlafaxine XR 75 to 225 mg/day was compared with fluoxetine 20
to 60 mg/day in patients with major depression in 2 randomized,
double-blind, placebo-controlled, multicenter studies. Remission rates
were significantly in favor of venlafaxine XR recipients in one study: 37,
22 and 18% of patients treated with venlafaxine XR, fluoxetine or placebo,
resp., achieved full remission (HAM-D total score ≤ 7 at end-point).
In the other trial, venlafaxine XR and fluoxetine had comparable efficacy
in reducing HAM-D and Hamilton Rating Scale for Anxiety (HAM-A) total
scores compared with placebo. However, the HAM-A response rate was
significantly higher with venlafaxine XR than with fluoxetine at week 12.
In a comparative study involving paroxetine, redns. from baseline in HAM-D
and MADRS total scores in patients given venlafaxine XR 75 mg/day or
paroxetine 20 mg/day for 12 wk were significant, but no significant
differences between treatment groups were evident. Discontinuation rates
because of unsatisfactory clin. response were similar among patients
treated with venlafaxine XR, fluoxetine or paroxetine. Adverse events
pertaining to the digestive (nausea, dry mouth), nervous (dizziness,
somnolence, insomnia) and urogenital (abnormal ejaculation) systems as
well as sweating were the most frequently reported adverse events during 8

to 12 wk of treatment in 3 randomized, double-blind, multicenter trials. Comparative studies with fluoxetine and paroxetine demonstrated a similar adverse event profile to venlafaxine XR. Conclusion: Venlafaxine XR has shown efficacy in the treatment of major depression and was at least as effective as fluoxetine or paroxetine and more effective than venlafaxine IR. Furthermore, it is effective at reducing symptoms of anxiety in depressed patients. The incidence of adverse events in recipients of venlafaxine XR is similar to that in patients receiving treatment with well established selective serotonin reuptake inhibitors. As an effective and well tolerated antidepressant, venlafaxine XR should be considered as a first-line pharmacol. treatment in patients with major depression.

CC 1-0 (Pharmacology)

IT **Mental disorder**

(major **depression**; pharmacodynamics, pharmacokinetics, efficacy and tolerability of venlafaxine extended-release in humans with major **depression** with associated anxiety)

IT **93413-69-5, Venlafaxine**

RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(pharmacodynamics, pharmacokinetics, efficacy and tolerability of venlafaxine extended-release in humans with major **depression** with associated anxiety)

REFERENCE COUNT: 125 THERE ARE 125 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 262 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2001:715984 HCAPLUS

DOCUMENT NUMBER: 136:31584

TITLE: Venlafaxine in the treatment of postpartum depression

AUTHOR(S): Cohen, Lee S.; Viguera, Adele C.; Bouffard, Suzanne M.; Nonacs, Ruta M.; Morabito, Cassandra; Collins, Mary H.; Ablon, J. Stuart

CORPORATE SOURCE: Perinatal and Reproductive Psychiatry Clinical Research Program, Department of Psychiatry, Harvard Medical School, Massachusetts General Hospital, Boston, MA, 02114, USA

SOURCE: Journal of Clinical Psychiatry (2001), 62(8), 592-596
CODEN: JCLPDE; ISSN: 0160-6689

PUBLISHER: Physicians Postgraduate Press, Inc.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Although postpartum depression is a highly prevalent illness, antidepressant treatment studies of postpartum depression are sparse. Incomplete recognition and treatment of puerperal illness place women at risk for chronic depression and may have adverse effects on child development. An 8-wk, flexible-dose, open study of venlafaxine (immediate release; mean dose = 162.5 mg/day) was performed in a group of 15 women who met DSM-III-R criteria for major depressive disorder with onset within the first 3 mo postpartum. Patients were assessed at baseline and every 2 wk across the study. Measurements of outcome included the 17-item Hamilton Rating Scale for Depression (HAM-D), the Kellner Symptom Questionnaire, and the Clin. Global Impressions scale (CGI). Despite baseline scores of depression that were particularly high, response to treatment was robust. Twelve of 15 patients experienced remission of major depression (HAM-D score ≤ 7 or CGI score ≤ 2). Dramatic decrease in anxiety paralleled the decrease in depression across the sample. Venlafaxine is effective in the treatment of postpartum major

depression. Early identification of women who suffer from postpartum mood disturbance is critical to minimize the morbidity associated with untreated mood

disturbance and the effect of depression on children and families.

CC 1-11 (Pharmacology)

IT **Mental disorder**

(major **depression**, postpartum; venlafaxine in treatment of postpartum **depression** in women)

IT 93413-69-5, Venlafaxine

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(venlafaxine in treatment of postpartum **depression** in women)

REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 263 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2001:606308 HCAPLUS

DOCUMENT NUMBER: 135:352671

TITLE: Efficacy of venlafaxine extended release in patients with major depressive disorder and comorbid generalized anxiety disorder

AUTHOR(S): Silverstone, Peter H.; Salinas, Eliseo

CORPORATE SOURCE: Department of Psychiatry, University of Alberta, Edmonton, AB, T6G 2B7, Can.

SOURCE: Journal of Clinical Psychiatry (2001), 62(7), 523-529
CODEN: JCLPDE; ISSN: 0160-6689

PUBLISHER: Physicians Postgraduate Press, Inc.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB A subset of patients with comorbid major depressive disorder and generalized anxiety disorder (GAD) was examined from a double-blind, placebo-controlled study comparing the efficacy and safety of venlafaxine extended release (XR) and fluoxetine. From a total of 368 patients, 92 patients meeting DSM-IV criteria for major depressive disorder who also had comorbid GAD were identified. The comparison group comprised 276 evaluable non-comorbid patients. Patients received venlafaxine XR (75-225 mg/day), fluoxetine (20-60 mg/day), or placebo for 12 wk. Efficacy evaluations included Hamilton Rating Scale for Depression (HAM-D), Hamilton Rating Scale for Anxiety (HAM-A), and Clin. Global Impressions (CGI) scale. By the final assessment at week 12, comorbid patients in the venlafaxine XR group, but not in the fluoxetine group, showed a significantly greater decrease than those in the placebo group in the primary efficacy variables of mean HAM-D and HAM-A total scores ($p < .05$, pairwise comparison). In comorbid patients, significant pairwise differences were noted between venlafaxine XR and placebo at week 12 for the secondary variables of HAM-D anxiety-somatization and retardation factors, HAM-D depressed mood item, HAM-A psychic anxiety factor, the Hospital Anxiety and Depression scale (HAD) anxiety subscale score, and the Covi Anxiety Scale score. Fluoxetine was significantly different from placebo only on the HAD depression subscale score. Response, defined as $\geq 50\%$ decrease in symptoms score, was achieved in 66% and 59% of the comorbid patients for HAM-D and HAM-A, resp., in the venlafaxine XR group at week 12. This response was higher than that seen with fluoxetine (52% and 45%) or placebo (36% and 24%). Onset of efficacy appeared to be slower in comorbid than in non-comorbid patients. This is the first evidence from a controlled study of the effectiveness of pharmacotherapy in patients with comorbid major depressive disorder and GAD. The delayed improvement in comorbid patients compared with non-comorbid patients suggests that a longer treatment period may be necessary in comorbid

patients.

CC 1-11 (Pharmacology)

IT **Mental disorder**

(**depression**, major; efficacy of venlafaxine extended release and fluoxetine in humans with major depressive disorder and comorbid generalized anxiety disorder)

IT 54910-89-3, Fluoxetine **93413-69-5**, Venlafaxine

RL: **BAC (Biological activity or effector, except adverse)**; BSU

(Biological study, unclassified); **THU (Therapeutic use)**; BIOL

(Biological study); **USES (Uses)**

(efficacy of venlafaxine extended release and fluoxetine in humans with major **depressive** disorder and comorbid generalized anxiety disorder)

REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 264 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2001:813918 HCAPLUS

DOCUMENT NUMBER: 137:119423

TITLE: Association Study of the 5-HT6 Receptor Polymorphism (C267T) and Symptomatology and Antidepressant Response in Major Depressive Disorders

AUTHOR(S): Wu, Wei-Hsin; Huo, Sheue-Jane; Cheng, Chih-Ya; Hong, Chen-Jee; Tsai, Shih-Jen

CORPORATE SOURCE: Cheng Hsin Rehabilitation and Medical Center, Division of Psychiatry, Veterans General Hospital-Taipei, Taipei, Taiwan

SOURCE: Neuropsychobiology (2001), 44(4), 172-175

CODEN: NPBIAL; ISSN: 0302-282X

PUBLISHER: S. Karger AG

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The serotonergic neurotransmitter system has been implicated in the pathogenesis of major depressive disorder (MDD). Of the 14 human serotonin (5-HT) receptors, the 5-HT6 receptor may be a candidate for the study of MDD because of its relative abundance in certain limbic areas and its high affinity to several antidepressants. The present study tested the hypothesis that a 5-HT6 genetic polymorphism (C267T) is associated with the clin. manifestations of, and/or antidepressant response in, MDD. The Hamilton Depression Rating Scale was used to assess 57 MDD patients before antidepressant treatment, with 34 patients completing the 4-wk treatment and evaluation. The results of the association study provide that the 5-HT6 C267T genetic variant does not play a major role in producing the clin. manifestations or antidepressant response for MDD patients. Further study with a functional 5-HT6 polymorphism is needed to explore the role of 5-HT6 in the pathogenesis of MDD.

CC 1-11 (Pharmacology)

Section cross-reference(s): 14

IT **Mental disorder**

(major **depression**; association study of the 5-HT6 receptor polymorphism (C267T) and symptomatol. and antidepressant response in major depressive disorders)

IT 54910-89-3, Fluoxetine **93413-69-5**, Venlafaxine

RL: **PAC (Pharmacological activity)**; **THU (Therapeutic use)**; BIOL (Biological study); **USES (Uses)**

(association study of the 5-HT6 receptor polymorphism (C267T) and symptomatol. and antidepressant response in major **depressive** disorders)

REFERENCE COUNT: 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 265 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2001:622393 HCAPLUS

DOCUMENT NUMBER: 135:339134

TITLE: Adjunctive dopamine agonists in treatment-resistant
Bipolar II depression: an open case seriesAUTHOR(S): Perugi, G.; Toni, C.; Ruffolo, G.; Frare, F.; Akiskal,
H.CORPORATE SOURCE: Department of Psychiatry, University of Pisa, Pisa,
Italy

SOURCE: Pharmacopsychiatry (2001), 34(4), 137-141

CODEN: PHRMEZ; ISSN: 0176-3679

PUBLISHER: Georg Thieme Verlag

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Objective: Previous studies and case observations have suggested that dopamine agonists (DAAs) such as pramipexole (PPX) and ropinirole (RPN) might be effective for major depression, but their adjunctive use in treatment-resistant bipolar II depression has not yet been specifically addressed. Method: A chart review was conducted on 18 patients with a DSM-III-R bipolar NOS (Bipolar II) major depressive episode who were admitted to the day-hospital of the Department of Psychiatry at the University of Pisa. DAAs were added to ongoing treatments with conventional antidepressants and mood stabilizers to which patients had not responded after a period of at least 8 wk. Clin. state and adverse effects were assessed at each visit. Final improvement in CGI scores of 1 or 2 were considered as responders. Results: Mean DAA trial duration was 17.6 (sd = 7.8, range 4-34) weeks, with a mean final dose of 1.23 ± 0.32 mg/day (range, 0.75-1.50 mg/day) for PPX, and 2.97 ± 0.99 mg/day (range, 1.50-5.00 mg/day) for RPN. DAAs were well tolerated and did not show any neg. interaction with concomitant psychotropic medications. Only one patient became worse (final CGI = 5), and had to interrupt PPX due to nausea, increased agitation and irritability. Eight patients (44.4%) were considered responders (4 with PPX and 4 with RPN): 5 showed marked improvement (CGI = 1), and 3 showed moderate improvement (CGI = 2); another 5 (27.8%) manifested a transient response not sustained up to the end. The initial and final scores of CGI severity scale for all patients (responders and non-responders combined) were, resp., 5.33 ± 0.7 and 3.94 ± 1.3 (mean \pm S.D). The mean change according to the CGI severity scale was statistically significant ($t = 4.74$, $p < 0.0002$). Conclusion: From the results, PPX and RPN appear to be well tolerated and potentially useful in the adjunctive treatment of drug-resistant bipolar II depression.

CC 1-11 (Pharmacology)

IT **Mental disorder**

(manic bipolar disorder; adjunctive dopamine agonists in treatment-resistant bipolar II **depression** in humans who had been previously treated with traditional mood stabilizers and antidepressants)

IT 50-47-5, Desipramine 50-48-6, Amitriptyline 50-49-7, Imipramine
58-39-9, Perfenazine 72-69-5, Nortriptyline 99-66-1 298-46-4,
Carbamazepine 7439-93-2, Lithium, biological studies 54739-18-3,
Fluvoxamine 59729-33-8, Citalopram 60142-96-3, Gabapentin
61869-08-7, Paroxetine 79617-96-2, Sertraline 84057-84-1, Lamotrigine
91374-21-9, Ropinirole 93413-69-5, Venlafaxine 104632-26-0,
Pramipexole

RL: **BAC** (Biological activity or effector, except adverse); BSU
(Biological study, unclassified); **THU** (Therapeutic use); BIOL

(Biological study); USES (Uses)

(adjunctive dopamine agonists in treatment-resistant bipolar II **depression** in humans who had been previously treated with traditional mood stabilizers and antidepressants)

REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 266 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2001:311359 HCAPLUS

DOCUMENT NUMBER: 135:220442

TITLE: Algorithm for the treatment of chronic depression

AUTHOR(S): Trivedi, Madhukar H.; Kleiber, Beverly A.

CORPORATE SOURCE: Depression and Anxiety Disorders Program, Southwestern Medical Center at Dallas, The University of Texas, Dallas, TX, 75390-9101, USA

SOURCE: Journal of Clinical Psychiatry (2001), 62(Suppl. 6), 22-29

CODEN: JCLPDE; ISSN: 0160-6689

PUBLISHER: Physicians Postgraduate Press, Inc.

DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

AB A review with 41 refs. Chronic depression, which is marked by a course of illness lasting 2 yr or more, encompasses 4 subtypes of depressive illness: (1) chronic major depressive disorder, (2) dysthymic disorder, (3) dysthymic disorder with major depressive disorder ("double depression"), and (4) major depressive disorder with poor interepisodic recovery (i.e., in incomplete remission). In the 1990s, chronic depression had a reported prevalence rate of 3% to 5% and accounted for 30% to 35% of all cases of depression in the United States. The authors present an algorithm modified from the Texas Medication Algorithm Project for patients with chronic depression. This treatment algorithm recommends a progression of steps or stages in treating chronic depression. The first stage is monotherapy with the selective serotonin reuptake inhibitors, nefazodone, bupropion sustained release, venlafaxine extended release, mirtazapine, or psychotherapy. Later options include combination therapy, electroconvulsive therapy, atypical antipsychotics, and novel treatments. Utilization of a comprehensive treatment algorithm for chronic major depression should encourage efficient, efficacious treatment.

CC 1-0 (Pharmacology)

IT **Mental disorder**

(**depression**; algorithm for treatment of chronic **depression** in humans)

IT 34911-55-2, bupropion 83366-66-9, nefazodone 85650-52-8, mirtazapine 93413-69-5, venlafaxine

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(algorithm for treatment of chronic **depression** in humans)

REFERENCE COUNT: 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 267 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2000:98327 HCAPLUS

DOCUMENT NUMBER: 132:146650

TITLE: Treating depression with a combination of a serotonin uptake inhibitor, a 5-HT1A presynaptic antagonist, and a 5-HT1A agonist

INVENTOR(S): Depoortere, Henri

PATENT ASSIGNEE(S): Sanofi-Synthelabo, Fr.
 SOURCE: PCT Int. Appl., 36 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: French
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000006160	A1	20000210	WO 1999-FR1825	19990726
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
FR 2781671	A1	20000204	FR 1998-9603	19980728
AU 9949167	A1	20000221	AU 1999-49167	19990726
PRIORITY APPLN. INFO.:			FR 1998-9603	A 19980728
			WO 1999-FR1825	W 19990726
AB	Pharmaceutical compns. are provided which contain a serotonin uptake inhibitor (e.g. fluoxetine), a 5-HT1A presynaptic antagonist (e.g. pindolol), and a 5-HT1A agonist (e.g. buspirone) as a combination product for simultaneous, sep., or prolonged use for treating various forms of depression.			
IC	ICM A61K031-40 ICS A61K031-135; A61K031-505; A61K031-135; A61K031-505			
CC	1-11 (Pharmacology) Section cross-reference(s): 63			
IT	Mental disorder (depression, major; serotonin uptake inhibitor-5-HT1A presynaptic antagonist-5-HT1A agonist combination for treatment of depression)			
IT	Mental disorder (depression, neurotic; serotonin uptake inhibitor-5-HT1A presynaptic antagonist-5-HT1A agonist combination for treatment of depression)			
IT	Mental disorder (manic bipolar disorder; serotonin uptake inhibitor-5-HT1A presynaptic antagonist-5-HT1A agonist combination for treatment of depression)			
IT	Mental disorder (obsession-compulsion; serotonin uptake inhibitor-5-HT1A presynaptic antagonist-5-HT1A agonist combination for treatment of depression)			
IT	Mental disorder (phobia, social; serotonin uptake inhibitor-5-HT1A presynaptic antagonist-5-HT1A agonist combination for treatment of depression)			
IT	13523-86-9, Pindolol 36505-84-7, Buspirone 54739-18-3, Fluvoxamine 54910-89-3, Fluoxetine 59729-33-8, Citalopram 61869-08-7, Paroxetine 71827-56-0, Clemeprol 79617-96-2, Sertraline 83366-66-9, Nefazodone 83455-48-5, Bromerguride 83928-76-1, Gepirone 87760-53-0, Tandospirone 90494-76-1, SR 57746 92623-85-3, Milnacipran 93413-69-5, Venlafaxine 95847-70-4, Ipsapirone 98206-10-1, Flesinoxan			

99487-26-0, MCI 225 102908-59-8, Binospirone 112922-55-1, Cericlamine
114298-18-9, Zalospirone 119356-77-3, Dapoxetine 127266-56-2, WY 50324
132449-45-7, E4414 132449-46-8, Lesopitron 132501-12-3, WY 48723
132873-35-9, LY 274600 133109-86-1, EMD 56551 135722-27-9, S 14671
138298-79-0, Alnespirone 141318-62-9, LY 293284 142348-14-9,
Pyricapirone 144340-02-3, CP 119333 144980-77-8, BAYx 3702
145969-30-8, OPC 14523 146479-45-0, BMS 181101 146998-34-7, S 15535
149494-37-1, Ebalzotan 149654-41-1, U 92016A 150019-94-6, BMS 184111
150527-35-8, FG 5865 150710-80-8, HT 90B 156896-33-2, LY 301317
161178-10-5, YM 35992 161312-09-0 162408-66-4, GR 103691
162581-80-8, LY 297996 163521-12-8, EMD 68843 167933-07-5, Flibanserin
177975-08-5, EMD 77697 179756-58-2, F 11440 208516-87-4, NAD 299
214686-27-8, F 12439 221452-76-2, EF 7412 257614-79-2 257863-96-0,
NS 2389 257863-98-2, EMD 80084 257864-13-4, AP 521 257864-15-6, AZ
16596 257864-30-5, DDR 203901 257864-31-6, DDR 205852 257864-33-8,
DDR 208978 257864-35-0, DDR 211278 257864-36-1, DDR 212219
257864-37-2, FCE 23892 257864-38-3, LY 315535 257864-39-4, S 215521
257864-41-8, WAY 100802 257864-47-4, EMD 67478

RL: **BAC (Biological activity or effector, except adverse)**; BSU
(Biological study, unclassified); **THU (Therapeutic use)**; BIOL
(Biological study); **USES (Uses)**

(serotonin uptake inhibitor-5-HT1A presynaptic antagonist-5-HT1A
agonist combination for treatment of **depression**)

REFERENCE COUNT: 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 268 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2000:558568 HCAPLUS

DOCUMENT NUMBER: 133:344483

TITLE: Efficacy of venlafaxine and predictors of response in
a prospective open-label study of patients with
treatment-resistant major depression

AUTHOR(S): Mitchell, Philip B.; Schweitzer, Isaac; Burrows,
Graham; Johnson, Gordon; Polonowita, Athula

CORPORATE SOURCE: School of Psychiatry, University of New South Wales,
Sydney, Australia

SOURCE: Journal of Clinical Psychopharmacology (2000), 20(4),
483-487

CODEN: JCPYDR; ISSN: 0271-0749

PUBLISHER: Lippincott Williams & Wilkins

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The aim of this study was to replicate the findings of a 1994 study, in
which a 30% response rate to venlafaxine was found in patients with
treatment-refractory depression, as well as to examine for any predictors
of such an outcome. The study was an 8-wk, open-label, prospective
investigation of venlafaxine in doses up to 300 mg in 312 patients
fulfilling criteria for either "absolute" or "relative" treatment resistance.
By week 8, 52.6% of the patients had responded, which was defined as a 50%
reduction in scores on the Montgomery-Asberg Depression Rating Scale; 49% of
those defined with "absolute resistance" demonstrated such an outcome.
Forty-five percent of the patients with absolute resistance who had failed to
respond to at least one tricyclic antidepressant responded to venlafaxine.
Response rates were higher in those with an absence (57.5%) compared with
the presence (31.0%) of any comorbid psychiatric disorder ($p < 0.001$),
"marked" (60.3%) compared with "mild or moderate" (51.6%) or "severe"
(43.4%) baseline ratings on the patient-rated Clin. Global Impressions
Scale ($p < 0.05$), and "relative" (61%) compared with "absolute" resistance
(49%) ($p = 0.06$). Furthermore, improvement in scores of 20% or 30% at

weeks 1 or 2 was associated with higher rates of final response ($p < 0.0005$). After logistic regression, both comorbid psychiatric illness ($p < 0.001$) and early improvement ($p < 0.0001$) remained significant and independent predictors of final response.

CC 1-11 (Pharmacology)

IT **Mental disorder**

(depression, major; efficacy of venlafaxine and predictors of response in prospective open-label study of patients with treatment-resistant major depression)

IT 93413-69-5, Venlafaxine

RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)

(efficacy of venlafaxine and predictors of response in prospective open-label study of patients with treatment-resistant major depression)

REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 269 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2000:214228 HCAPLUS

DOCUMENT NUMBER: 132:217027

TITLE: Randomized, double-blind comparison of venlafaxine and sertraline in outpatients with major depressive disorder

AUTHOR(S): Mehtonen, Olli-Pekka; Sogaard, Jesper; Roponen, Pekka; Behnke, Kirsten

CORPORATE SOURCE: Department of Biomedical Sciences, University of Tampere, Tampere, Finland

SOURCE: Journal of Clinical Psychiatry (2000), 61(2), 95-100
CODEN: JCLPDE; ISSN: 0160-6689

PUBLISHER: Physicians Postgraduate Press, Inc.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB This 8-wk, double-blind, randomized trial compared the efficacy and tolerability of venlafaxine and sertraline in patients with major depression. Outpatients ($N = 147$) with DSM-IV major depressive disorder and a baseline 21-item Hamilton Rating Scale for Depression (HAM-D) score of at least 18 were randomly assigned to venlafaxine, 37.5 mg b.i.d., or sertraline, 50 mg once daily. From day 15, the doses could be increased to venlafaxine, 75 mg b.i.d., or sertraline, 50 mg b.i.d. Efficacy was assessed with the 21-item HAM-D, the Montgomery-Asberg Depression Rating Scale (MADRS), and the Clin. Global Impressions scale (CGI) using a modified intent-to-treat anal. No significant differences were noted between treatments for mean HAM-D, MADRS, or CGI scores. At week 8, the HAM-D response rate was 83% with venlafaxine ($N = 75$) and 68% with sertraline ($N = 72$) ($p = .05$). A HAM-D score less than 10 was recorded in 68% of venlafaxine-treated and 45% of sertraline-treated patients at week 8 ($p = .008$). Among patients who increased their dose, the remission rate (HAM-D score < 10) was 67% with venlafaxine and 36% with sertraline at week 8 ($p < .05$). The overall discontinuation rate was 21% with venlafaxine and 17% with sertraline. The most common adverse events with venlafaxine were nausea, headache, and sweating and with sertraline were nausea, headache, and diarrhea. Among patients who increased their dose, approx. twice as many experienced a remission with venlafaxine, which is a more clin. relevant endpoint than response and represents the proportion of patients who have recovered or are well.

CC 1-11 (Pharmacology)

IT **Mental disorder**

(**depression**, major; comparison of venlafaxine and sertraline in outpatients with major depressive disorder)
 IT 79617-96-2, Sertraline 93413-69-5, Venlafaxine
 RL: ADV (Adverse effect, including toxicity); BAC (**Biological activity or effector, except adverse**); BSU (Biological study, unclassified); THU (**Therapeutic use**); BIOL (Biological study); USES (Uses)
 (comparison of venlafaxine and sertraline in outpatients with major depressive disorder)
 REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 270 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN
 ACCESSION NUMBER: 2000:260120 HCAPLUS
 DOCUMENT NUMBER: 132:274257
 TITLE: Double-blind comparison of venlafaxine and amitriptyline in outpatients with major depression with or without melancholia
 AUTHOR(S): Gentil, Valentim; Kerr-Correa, Florence; Moreno, Ricardo; Busnello, Ellis D'Arrigo; De Campos, Joao Alberto; Juruena, Mario Francisco; Lafer, Beny; Moreno, Doris Hupfeld; De Cassia Rodrigues Rosa, Lucena; Tiosso, Ana; Benedictis, Eliana
 CORPORATE SOURCE: Universidade de Sao Paulo, Sao Paulo, Universidade do Estado de Sao Paulo, Botucatu, Brazil
 SOURCE: Journal of Psychopharmacology (London) (2000), 14(1), 61-66
 CODEN: JOPSEQ; ISSN: 0269-8811
 PUBLISHER: SAGE Publications
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 AB The purpose of this study was to compare the efficacy and tolerability of venlafaxine and amitriptyline in outpatients with major depression with or without melancholia. This was an 8-wk, multicenter, randomized, double-blind, parallel-group comparison of venlafaxine and amitriptyline. Outpatients with DSM-IV major depression, a min. score of 20 on the 21-item Hamilton Depression Rating Scale (HAM-D), and depressive symptoms for at least 1 mo were eligible. Patients were randomly assigned to venlafaxine or amitriptyline, both drugs titrated to a maximum of 150 mg/day until study day 15. The primary efficacy variables were the final on-therapy scores on the HAM-D, Montgomery-Asberg Depression Rating Scale and Clin. Global Impression severity scales. Data were evaluated on an intent-to-treat basis using the LOCF method. One hundred and 16 patients were randomized, and 115 were evaluated for efficacy. Both drugs showed efficacy in the treatment of depression with or without melancholia. No significant differences were noted between treatments for any efficacy parameter. However, significantly ($p < 0.05$) more patients in the amitriptyline group had at least one adverse event. These results should support the efficacy and tolerability of venlafaxine in comparison with amitriptyline for treating major depression with or without melancholia.
 CC 1-11 (Pharmacology)
 IT **Mental disorder**
 (**depression**, major; venlafaxine vs. amitriptyline in outpatient humans with major **depression** with or without melancholia)
 IT 50-48-6, Amitriptyline 93413-69-5, Venlafaxine
 RL: ADV (Adverse effect, including toxicity); BAC (**Biological activity or effector, except adverse**); BSU (Biological study, unclassified); THU (**Therapeutic use**); BIOL (Biological study);

USES (Uses)

(venlafaxine vs. amitriptyline in outpatient humans with major depression with or without melancholia)

REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 271 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1999:632087 HCAPLUS

DOCUMENT NUMBER: 131:331980

TITLE: Differential effect of chronic antidepressant treatments on lipopolysaccharide-induced depressive-like behavioural symptoms in the rat

AUTHOR(S): Shen, Yan; Connor, Thomas J.; Nolan, Yvonne; Kelly, John P.; Leonard, Brian E.

CORPORATE SOURCE: Department of Pharmacology, National University of Ireland, Galway, Ire.

SOURCE: Life Sciences (1999), 65(17), 1773-1786

CODEN: LIFSAK; ISSN: 0024-3205

PUBLISHER: Elsevier Science Inc.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB In the present study we observed that lipopolysaccharide (LPS) administration provoked a characteristic reduction in body weight gain, food consumption, saccharin (but not water) consumption and nocturnal locomotor activity. It has been previously suggested that the ability of LPS to suppress the consumption of, and preference for, a palatable solution such as saccharin without altering water consumption, may represent an anhedonic response. The results of the present study demonstrate that chronic treatment with the tricyclic antidepressant (TCA) desipramine (7.5 mg/kg; i.p.) prevented LPS-induced anorexia, loss of body weight, the antidipsogenic effect and hypoactivity. In contrast, chronic treatment with the antidepressants paroxetine (7.5 mg/kg; i.p.) and venlafaxine (10 mg/kg; i.p.) failed to alter any of the LPS-induced behavioral responses. Furthermore, chronic treatment with desipramine (and to a lesser extent paroxetine) reduced the consumption of, and preference for, saccharin suggesting that these antidepressant treatments induce an "anhedonic" response in their own right. In conclusion, chronic desipramine treatment attenuated LPS-induced depressive-like behavioral symptoms in the rat. However, chronic treatment with paroxetine and venlafaxine did not significantly alter LPS-induced behavioral responses. The results of the present study support the hypothesis that TCA's may exert part of their anti-depressive efficacy through their effects on the immune system. However, this property does not appear to be shared by newer antidepressants which possess a better side effect profile than the TCA's. The suppressive effect of TCA's on proinflammatory cytokine secretion is discussed as a mechanism by which these agents alter LPS-induced behavioral responses.

CC 1-11 (Pharmacology)

Section cross-reference(s): 14, 15

IT **Mental disorder**

(depression; effect of chronic antidepressant treatments on LPS-induced depressive-like behavioral symptoms in the rat)

IT 50-47-5, Desipramine 61869-08-7, Paroxetine 93413-69-5, Venlafaxine

RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(effect of chronic antidepressant treatments on LPS-induced depressive-like behavioral symptoms in the rat)

REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 272 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1999:204308 HCAPLUS

DOCUMENT NUMBER: 131:627

TITLE: The determination of the optimal dose of milnacipran
in the olfactory bulbectomized rat model of depression

AUTHOR(S): Redmond, Anna M.; Kelly, John P.; Leonard, Brian E.

CORPORATE SOURCE: Department of Pharmacology, National University of
Ireland, Galway, Ire.

SOURCE: Pharmacology, Biochemistry and Behavior (1999), 62(4),
619-623

CODEN: PBBHAU; ISSN: 0091-3057

PUBLISHER: Elsevier Science Inc.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Olfactory bulbectomy (OB) is associated with a variety of behavioral
abnormalities such as hyperactivity in the "open-field" test. Previous
studies have shown that chronic administration of antidepressants can
reverse this behavioral deficit. The activity of milnacipran (20, 30, and
40 mg/kg, PO bid) administered in two equally divided doses twice daily
was assessed in the olfactory bulbectomized rat model of depression. It
was found that chronic treatment with milnacipran at the doses of 30 and
40 mg/kg, but not 20 mg/kg, attenuated the lesion-induced hyperactivity of
the OB rat in the "open-field" test following 14 days of treatment. In
the step-through passive avoidance test, administration of milnacipran at
doses of 20, 30, and 40 mg/kg had no effect on the performance deficit
associated with olfactory bulbectomy. Olfactory bulbectomy reduced the
concentration of noradrenaline (NA) in the frontal cortex. However, chronic
milnacipran treatment did not significantly alter this deficit. It is
concluded that milnacipran, when administered chronically at doses of 30
and 40 mg/kg, is effective at reversing the "open-field" deficit associated
with olfactory bulbectomy, and that a dose of 30 mg/kg is an optimal dose.

CC 1-11 (Pharmacology)

IT **Mental disorder**

(**depression**; optimal dose of milnacipran in olfactory
bulbectomized model of **depression**)

IT 92623-85-3, Milnacipran

RL: **BAC (Biological activity or effector, except adverse)**; BSU
(Biological study, unclassified); **THU (Therapeutic use)**; BIOL
(Biological study); **USES (Uses)**

(optimal dose of milnacipran in olfactory bulbectomized model of
depression)

REFERENCE COUNT: 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 273 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1999:657043 HCAPLUS

DOCUMENT NUMBER: 131:266963

TITLE: Venlafaxine in treatment-resistant major depression: a
Canadian multicenter, open-label trial

AUTHOR(S): De Montigny, Claude; Silverstone, Peter H.; Debonnel,
Guy; Blier, Pierre; Bakish, David

CORPORATE SOURCE: Neurobiological Psychiatry Unit, Department of
Psychiatry, McGill University, Montreal, QC, H3A 1A1,
Can.

SOURCE: Journal of Clinical Psychopharmacology (1999), 19(5),
401-406

CODEN: JCPYDR; ISSN: 0271-0749
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

AB This was an 8-wk, multicenter, open-label study of the efficacy and tolerability of venlafaxine in patients with treatment-resistant depression conducted in Canada. Inpatients or outpatients aged 18-70 yr with major depression were eligible if they had a 21-item Hamilton Rating Scale for Depression (HAM-D-21) score of ≥ 18 and a documented history of unsatisfactory improvement after a min. of 8 wk of treatment with an adequate dose of an antidepressant. Treatment with venlafaxine was started at 37.5 mg twice daily, and the dose could be titrated upward to a maximum of 375 mg/day during the 1st 4 wk on the basis of the investigator's assessment of clin. response and tolerability. Of the 159 patients enrolled, 152 were evaluable for efficacy. The mean daily venlafaxine dose was 260 mg/day. The mean HAM-D-21 score decreased by 52%, and the mean Montgomery-Asberg Depression Rating Scale score decreased by 50% from basal values to day 56. A response (50% improvement from basal values of the HAM-D-21) was achieved by 58% of the patients, and a remission ($\geq 75\%$ improvement in the HAM-D-21) was observed in 28% at day 56. By day 56, 88% of the patients had improved on the Clin. Global Impression Improvement scale. Only 8% of the patients discontinued for adverse events. The most common adverse events were headache, insomnia, nausea, constipation, diaphoresis, and xerostomia. These results suggest that venlafaxine is effective and well tolerated for the management of patients with treatment-resistant major depression.

CC 1-11 (Pharmacology)

IT **Mental disorder**

(**depression**; venlafaxine effect in treatment-resistant major depression of humans)

IT 93413-69-5, Venlafaxine

RL: ADV (Adverse effect, including toxicity); **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)

(venlafaxine effect in treatment-resistant major **depression** of humans)

REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 274 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1999:743266 HCAPLUS

DOCUMENT NUMBER: 132:206027

TITLE: Noradrenaline (norepinephrine) and depression: Role in etiology and therapeutic implications

AUTHOR(S): Van Moffaert, Myriam; Dierick, Michel

CORPORATE SOURCE: Department of Psychiatry and Psychosomatic Medicine, University of Ghent, Ghent, Belg.

SOURCE: CNS Drugs (1999), 12(4), 293-305

CODEN: CNDREF; ISSN: 1172-7047

PUBLISHER: Adis International Ltd.

DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

AB A review, with 47 refs. In the pharmacol. treatment of depression the focus has recently shifted from serotonin (5-hydroxytryptamine; 5-HT) to noradrenaline (norepinephrine), with the advent of new antidepressants such as noradrenaline reuptake inhibitors, noradrenergic and selective serotonergic antidepressants, and serotonin/noradrenaline reuptake inhibitors. It has been suggested that noradrenergic compds. may prove to

have beneficial activity in those depressions that are characterized by a 'noradrenergic deficiency syndrome', which is clin. manifested through emotional withdrawal, psychomotor retardation, as well as concentration and memory deficits. The role of noradrenergic mechanisms in the etiol. of depression has been assumed since the catecholamine hypothesis, based on the inhibitory action of tricyclic antidepressants and monoamine oxidase inhibitors on noradrenaline uptake, was formulated. In this article, the etiol. significance of noradrenaline in depression is discussed with regard to the anatomical basis of the noradrenergic system (the locus ceruleus), noradrenaline metabolites, noradrenergic receptors, some aspects of thyroid function and the hypothalamic-pituitary-adrenal axis. The efficacy and tolerability profiles of new antidepressant compds. reboxetine, milnacipran, mirtazapine and venlafaxine are discussed in view of their noradrenergic activity.

CC 14-0 (Mammalian Pathological Biochemistry)

Section cross-reference(s): 1, 2

IT **Mental disorder**

(**depression**; noradrenaline in **depression** in human)

IT 71620-89-8, Reboxetine 85650-52-8, Mirtazapine 92623-85-3,
Milnacipran 93413-69-5, Venlafaxine

RL: **BAC (Biological activity or effector, except adverse)**; BSU

(Biological study, unclassified); **THU (Therapeutic use)**; BIOL

(Biological study); **USES (Uses)**

(noradrenaline in **depression** in human)

REFERENCE COUNT: 48 THERE ARE 48 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 275 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1999:587401 HCAPLUS

DOCUMENT NUMBER: 131:208372

TITLE: Antidepressant treatment of the depressed patient with
insomnia

AUTHOR(S): Thase, Michael E.

CORPORATE SOURCE: Department of Psychiatry, University of Pittsburgh
School of Medicine, Pittsburgh, PA, 15213, USA

SOURCE: Journal of Clinical Psychiatry (1999), 60(Suppl. 17),
28-31

CODEN: JCLPDE; ISSN: 0160-6689

PUBLISHER: Physicians Postgraduate Press, Inc.

DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

AB A review with 8 refs. Sleep disturbances are an integral part of depressive disorder. As such, they are a part of all contemporary sets of diagnostic criteria for major depression and of all major symptom-based rating scales for depression. Insomnia is a particularly frequent complaint, and it is reported by more than 90% of depressed patients. Although the "kindling" or "illness transduction" model of depression remains hypothetical, there is evidence that people with recurrent depression have more pronounced abnormalities of sleep neurophysiol. than those experiencing a single or initial episode. Therefore, early relief of insomnia in a depressed patient, in addition to alleviating other symptoms, may increase adherence to treatment and increase daytime performance and overall functioning, while complete relief of insomnia may improve prognosis. Stimulation of serotonin-2 (5-HT₂) receptors is thought to underlie insomnia and changes in sleep architecture seen with selective serotonin reuptake inhibitors (SSRIs) or serotonin-norepinephrine reuptake inhibitors (SNRIs). This is the reason why hypnotics or low-dose trazodone are commonly coprescribed at the initiation of the treatment with either the SSRIs or SNRIs. On the other

hand, antidepressant drugs with 5-HT₂ blocking properties, such as mirtazapine or nefazodone, alleviate insomnia and improve sleep architecture. In depressed patients, mirtazapine produces a significant shortening of sleep-onset latency, increases a total sleep time, and leads to a marked improvement in sleep efficiency. Antidepressants with preferential 5-HT₂ blocking properties are therefore a good treatment option for depressed patients with marked insomnia.

CC 1-0 (Pharmacology)

IT **Mental disorder**

(**depression**; antidepressant treatment of depressed humans with insomnia)

IT 83366-66-9, Nefazodone 85650-52-8, Mirtazapine 93413-69-5, Venlafaxine

RL: **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(antidepressant treatment of **depressed** humans with insomnia)

REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 276 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1999:678448 HCAPLUS

DOCUMENT NUMBER: 132:161106

TITLE: The effect of milnacipran on depressive symptoms

AUTHOR(S): Silva, J. A. Costa E.

CORPORATE SOURCE: World Psychiatric Association Council Member and Past President, Rio de Janeiro, S 22461, Brazil

SOURCE: International Journal of Psychiatry in Clinical Practice (1999), 3(Suppl. 2), S21-S27
CODEN: IJPCFZ; ISSN: 1365-1501

PUBLISHER: Martin Dunitz Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Existing evidence suggests that depression occurs due to a dysfunction in more than one neurotransmitter system, leading to particular depressive symptoms which relate to a component of the disorder. Thus, antidepressants exerting an effect on more than one neurotransmitter system provide a therapeutic benefit for a wide range of patients. The effect of 100 mg milnacipran daily on various signs and symptoms of depression associated with the activity of serotonergic and/or noradrenergic pathways was examined in three placebo-controlled studies, using the individual items and clusters from the Hamilton Depression Rating Scale (HDRS) and the Montgomery Asberg Depression Rating Scale (MADRS). Improvements in individual depressive symptoms as well as the global depression score were examined (total score reduction for milnacipran and placebo: 13.2 and 10.2 [HDRS] and 16.6 and 11.9 [MADRS]). Addnl., milnacipran improved various presentations of depression, including hospitalized depression (total score reduction for milnacipran and placebo: 15.2 and 9.1 [HDRS] and 19.3 and 12.2 [MADRS]). It is concluded that milnacipran, through its dual mechanism of action on serotonin and noradrenaline neurotransmission, produces a widespread parallel improvement in all depressive symptoms.

CC 1-11 (Pharmacology)

IT **Mental disorder**

(**depression**, symptoms; milnacipran effect on depressive symptoms)

IT 92623-85-3, Milnacipran

RL: **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(milnacipran effect on **depressive** symptoms)

REFERENCE COUNT: 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 277 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1998:706088 HCAPLUS
DOCUMENT NUMBER: 129:310902
TITLE: Composition for treating pain using a cyano-oxime
compound and a synergistic analgesic agent
INVENTOR(S): Mitch, Charles Howard; Sauerberg, Per; Shannon, Harlan
Edgar
PATENT ASSIGNEE(S): Eli Lilly and Co., USA
SOURCE: PCT Int. Appl., 26 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9846227	A1	19981022	WO 1998-US7293	19980410
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9869669	A1	19981111	AU 1998-69669	19980410
EP 1007041	A1	20000614	EP 1998-915497	19980410
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2002503224	T2	20020129	JP 1998-544126	19980410
PRIORITY APPLN. INFO.:			US 1997-43574P	P 19970411
			WO 1998-US7293	W 19980410

OTHER SOURCE(S): MARPAT 129:310902

AB The invention provides a composition useful for the treatment of pain, wherein the composition comprises (R1)(R3)C=NR2 [R1 = I (r = 2-4; s = 1, 2; t = 0, 1); R2 = OR4 (R4 = C1-4 alkyl, C2-4 alkenyl, C2-4 alkynyl), OCOR5 (R5 = H, R4); R3 = CN] and a synergistic analgesic.

IC ICM A61K031-44

CC 1-11 (Pharmacology)

Section cross-reference(s): 63

IT **Antidepressants**

(tricyclic; cyano-oxime compound and synergistic analgesic for composition for **pain treatment**)

IT 51-41-2, **Norepinephrine**

RL: BSU (Biological study, unclassified); BIOL (Biological study)
(mixed **serotonin-norepinephrine reuptake inhibitors**; cyano-oxime compound and synergistic analgesic for composition for pain treatment)

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 278 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1998:546953 HCAPLUS
DOCUMENT NUMBER: 129:285899

TITLE: Randomized, double-blind comparison of venlafaxine and fluoxetine in outpatients with major depression
 AUTHOR(S): E Silva, Jorge Costa
 CORPORATE SOURCE: University Rio de Janeiro, Rio de Janeiro, Brazil
 SOURCE: Journal of Clinical Psychiatry (1998), 59(7), 352-357
 CODEN: JCLPDE; ISSN: 0160-6689
 PUBLISHER: Physicians Postgraduate Press, Inc.
 DOCUMENT TYPE: Journal
 LANGUAGE: English

AB Background: This was an 8-wk, multicenter, randomized, double-blind, parallel-group study of the efficacy and tolerability of venlafaxine and fluoxetine. Method: Outpatients with DSM-III-R major depression, a min. score of 20 on the 21-item Hamilton Rating Scale for Depression (HAM-D), and depressive symptoms for at least 1 mo were eligible. Patients were randomly assigned to treatment with venlafaxine, 37.5 mg twice daily, or fluoxetine, 20 mg once daily. The dose could be increased to venlafaxine, 75 mg twice daily, or fluoxetine, 20 mg twice daily, after 3 wk for a poor response. The primary efficacy variables were the final on -therapy scores on the HAM-D, Montgomery-Asberg Depression Rating Scale (MADRS), and Clin. Global Impressions Severity of Illness (CGI-S) and Improvement (CGI-I) scales. Results: Three hundred eighty-two patients were randomly assigned to therapy and included in the intent-to-treat anal. Both venlafaxine and fluoxetine produced significant reduction from baseline to day 56 in mean HAM-D, MADRS, and CGI-S scores, but no significant differences were noted between groups. Among patients who increased their dose at 3 wk, significantly ($p < .05$) more patients taking venlafaxine than taking fluoxetine had a CGI-I score of 1 (very much improved) at the final evaluation. The most frequent adverse events were nausea, headache, and dizziness with venlafaxine and nausea, headache, and insomnia with fluoxetine. Conclusion: These results support the efficacy and tolerability of venlafaxine in comparison with fluoxetine for treating outpatients with major depression.

CC 1-11 (Pharmacology)

IT **Mental disorder**

(**depression**, major; venlafaxine vs. fluoxetine treatment of human outpatients with major **depression**)

IT 54910-89-3, Fluoxetine 93413-69-5, Venlafaxine

RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(venlafaxine vs. fluoxetine treatment of human outpatients with major **depression**)

L91 ANSWER 279 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1998:711927 HCAPLUS

DOCUMENT NUMBER: 130:119444

TITLE: A randomized, double-blind, parallel-group comparison of venlafaxine and clomipramine in outpatients with major depression

AUTHOR(S): Samuelian, J. C.; Hackett, David

CORPORATE SOURCE: CHU Timone, Marseille, Paris, Fr.

SOURCE: Journal of Psychopharmacology (London) (1998), 12(3), 273-278

CODEN: JOPSEQ; ISSN: 0269-8811

PUBLISHER: SAGE Publications

DOCUMENT TYPE: Journal

LANGUAGE: English

AB A multicenter, randomized, double-blind study was conducted to compare the

safety and antidepressant efficacy of venlafaxine and clomipramine in 102 outpatients with major depression. The patients received either venlafaxine or clomipramine at a dose titrated from 50mg to a maximum of 150 mg/day during the first 2 wk of treatment. Treatment was continued for up to 43 days. Montgomery Asberg Depression Rating Scale (MADRS) and Hamilton Depression Rating Scale (HAM-D) scores decreased significantly ($p \leq 0.05$) from baseline in each treatment group but were not significantly different between groups. Response rates on the MADRS and HAM-D were 62% and 59%, resp., with venlafaxine and 54% and 43%, resp., with clomipramine. Treatment-emergent study events were the primary reason for withdrawal in only 13% of venlafaxine-treated patients and 20% of clomipramine-treated patients. On questionnaires, the incidence of anticholinergic-type events was 60% with venlafaxine and 68% with clomipramine. However, significantly ($p=0.043$) more patients in the clomipramine group reported multiple anticholinergic events than in the venlafaxine group. In the clomipramine group, mean ventricular heart rate increased significantly ($p=0.003$) and mean systolic blood pressure decreased significantly ($p=0.028$) from baseline, but no clin. significant electrocardiog. changes were observed. These results confirm the efficacy and safety of venlafaxine in the treatment of outpatients suffering from major depression.

CC 1-11 (Pharmacology)

IT **Mental disorder**

(**depression**, major; venlafaxine vs. clomipramine treatment of human outpatients with major **depression**)

IT 303-49-1, Clomipramine 93413-69-5, Venlafaxine

RL: ADV (Adverse effect, including toxicity); **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)

(venlafaxine vs. clomipramine treatment of human outpatients with major **depression**)

REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 280 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1998:154276 HCAPLUS

DOCUMENT NUMBER: 128:239392

TITLE: Double-blind study of the efficacy and safety of milnacipran and imipramine in elderly patients with major depressive episode

AUTHOR(S): Tignol, J.; Pujol-Domenech, J.; Chartres, J. P.; Leger, J. - M.; Pletan, Y.; Tonelli, I.; Tournoux, A.; Pezous, N.

CORPORATE SOURCE: Department of Psychiatry, Hopital Charles Perrens, Bordeaux, 33076, Fr.

SOURCE: Acta Psychiatrica Scandinavica (1998), 97(2), 157-165
CODEN: APYSA9; ISSN: 0001-690X

PUBLISHER: Munksgaard International Publishers Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The novel antidepressant agent milnacipran is a dual and equipotent serotonin and noradrenaline reuptake inhibitor. The aim of this double-blind study was to compare the efficacy and safety of milnacipran (50 mg twice daily) with that of imipramine (50 mg twice daily) in elderly patients with major depressive episode. A total of 219 patients were randomly assigned to 8 wk of double-blind treatment with either milnacipran or imipramine; 72 patients withdrew from the study. At the end of treatment no significant differences were found between milnacipran

and imipramine in antidepressant efficacy. A significantly greater number of side-effects, particularly anticholinergic effects, was observed in the imipramine group. Milnacipran may be preferable to imipramine in elderly depressed patients, as it provides the same antidepressant activity as imipramine with a lower incidence of side-effects, and does not impair cognitive ability.

CC 1-11 (Pharmacology)

IT **Mental disorder**

(**depression**, major; milnacipran vs. imipramine efficacy and safety in elderly humans with major depressive episode)

IT 50-49-7, Imipramine 92623-85-3, Milnacipran

RL: ADV (Adverse effect, including toxicity); **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)

(milnacipran vs. imipramine efficacy and safety in elderly humans with major **depressive** episode)

REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 281 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1998:247944 HCAPLUS

DOCUMENT NUMBER: 128:303988

TITLE: A randomized, placebo-controlled, dose-response trial of venlafaxine hydrochloride in the treatment of major depression

AUTHOR(S): Rudolph, Richard L.; Fabre, Louis F.; Feighner, John P.; Rickels, Karl; Entsuah, Richard; Derivan, Albert T.

CORPORATE SOURCE: Clinical Res. Dev., Wyeth-Ayerst Res., Radnor, PA, USA

SOURCE: Journal of Clinical Psychiatry (1998), 59(3), 116-122

CODEN: JCLPDE; ISSN: 0160-6689

PUBLISHER: Physicians Postgraduate Press

DOCUMENT TYPE: Journal

LANGUAGE: English

AB We examine the efficacy and safety of three different dosages of venlafaxine hydrochloride (75, 225, and 375 mg/day) in a multicenter, randomized, double-blind, placebo-controlled, four-group study. Outpatients, 18 to 65 yr old, who met DSM-III criteria for major depression were included (N=358 randomized; 194 completed). Of the total patients completing the trial, 59%, 56%, 51%, and 51% were in the placebo, 75-mg, 225-mg, and 375-mg groups, resp. The primary outcome measures were the Hamilton Rating Scale for Depression (HAM-D21) total, HAM-D21 depression item, Montgomery-Asberg Depression Rating Scale total, and Clin. Global Impressions scale. Each dosage of venlafaxine was associated with statistically significant improvement as compared with placebo, based on the intent-to-treat sample. The two higher dosages were associated with a modestly greater antidepressant response that was the 75-mg dosage. Nausea, dizziness, somnolence, and anorexia were the most common adverse events attributable to venlafaxine. Since headache occurred at a similar frequency in both the drug and placebo groups, we did not consider it to be attributable to venlafaxine use. Withdrawal from the study due to adverse events occurred in 5%, 17%, 24%, and 30% of the patients in the placebo, 75-mg, 225-mg, and 375-mg groups, resp. In conclusion, venlafaxine, at dosages of 75-375 mg/day, is an effective and well-tolerated antidepressant. With increasing dosage, greater efficacy and possibly more adverse effects will occur.

CC 1-11 (Pharmacology)

IT **Mental disorder**

(**depression**, major; venlafaxine hydrochloride treatment of major **depression** in humans)

IT 99300-78-4, Venlafaxine hydrochloride

RL: ADV (Adverse effect, including toxicity); BAC (**Biological activity or effector, except adverse**); BSU (Biological study, unclassified); THU (**Therapeutic use**); BIOL (Biological study); USES (Uses)

(venlafaxine hydrochloride treatment of major **depression** in humans)

REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 282 OF 313 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1993:469623 HCAPLUS

DOCUMENT NUMBER: 119:69623

TITLE: Serotonin-2 receptor-mediated intraplatelet calcium mobilization in affective disorders. Relevance to the pathophysiology of depression

AUTHOR(S): Kusumi, Ichiro

CORPORATE SOURCE: Sch. Med., Hokkaido Univ., Sapporo, 060, Japan

SOURCE: Hokkaido Igaku Zasshi (1993), 68(3), 325-36

CODEN: HOIZAK; ISSN: 0367-6102

DOCUMENT TYPE: Journal

LANGUAGE: Japanese

AB 5-HT-stimulated intracellular Ca concentration change was studied in the platelets of healthy subjects, using fluorescent Ca indicator fura-2.

5-HT increased the Ca response in a concentration-dependent manner. The maximal

response was obtained at 10 μ M of 5-HT and its EC50 value was 0.4 μ M. This response was potently inhibited by selective 5-HT2 receptor antagonists, suggesting that the 5-HT-induced Ca mobilization is mediated by 5-HT2 receptors. This 5-HT-stimulated Ca response was not significantly affected by the time of blood sampling, gender, age, meal, or exercise. Therefore, it may be concluded that the 5-HT-induced Ca response in human platelets is a stable parameter and that it is suitable for assessing 5-HT2 receptor function in depressed patients. Thus, the 5-HT-induced Ca mobilization was measured in the platelets of depressed patients. The response was significantly higher in unmedicated patients with bipolar depression and melancholic major depression than in those with nonmelancholic major depression and normal controls. The enhanced Ca response to 5-HT failed to correlate with severity of depressive symptoms. In patients with bipolar depression and melancholic major depression, there was no significant difference in 5-HT-stimulated Ca response between unmedicated group and euthymic-treated group. These results suggest that 5-HT2 receptor function is increased in some type of affective disorders and that the enhanced Ca response to 5-HT may be trait dependent rather than state dependent.

CC 14-10 (Mammalian Pathological Biochemistry)

Section cross-reference(s): 1, 2

IT **Mental disorder**

(bipolar **depression**, 5-HT2 receptor function in, 5-HT-induced platelet calcium mobilization as marker for, of human)

IT **Mental disorder**

(major **depression**, 5-HT2 receptor function in, 5-HT-induced platelet calcium mobilization as marker for, of human)

IT 50-47-5, Desipramine 50-48-6, Amitriptyline 50-49-7, Imipramine
50-53-3, Chlorpromazine, biological studies 52-53-9, Verapamil
60-99-1, Levomepromazine 99-66-1, Valproic acid 117-89-5,
Trifluoperazine 146-48-5, Yohimbine 298-46-4, Carbamazepine

303-49-1, Clomipramine 439-14-5, Diazepam 749-02-0, Spiperone
 1622-61-3, Clonazepam 1893-33-0, Pipamperone 2062-78-4, Pimozide
 4199-09-1, (-)-Propranolol 5786-21-0, Clozapine 7439-93-2, Lithium,
 biological studies 10262-69-8, Maprotiline 14028-44-5, Amoxapine
 15676-16-1, Sulpiride 17692-51-2, Metergoline 24219-97-4, Mianserin
 26615-21-4, Zotepine 28981-97-7, Alprazolam 36505-84-7, Buspirone
 42399-41-7, Diltiazem 54739-18-3, Fluvoxamine 55985-32-5, Nicardipine
 74050-98-9, Ketanserin 75530-68-6, Nilvadipine 75558-90-6, Amperozide
 78950-78-4, 8-OH-DPAT 87051-43-2, Ritanserin 92623-85-3,
 Milnacipran 106266-06-2, Risperidone
 RL: ADV (Adverse effect, including toxicity); BAC (Biological
 activity or effector, except adverse); BSU (Biological study,
 unclassified); BIOL (Biological study)
 (serotonin-induced platelet calcium mobilization response to, of human,
 depression in relation to)

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ACCESSION NUMBER: 2005268855 EMBASE
 TITLE: [Dual-acting antidepressants].
 DUALNE PUSOBICI ANTIDEPRESIVA.
 AUTHOR: Ceskova E.
 CORPORATE SOURCE: Dr. E. Ceskova, Psychiatricka Klinika, LF MU, FN, Jihlavská
 20, 625 00 Brno - Bohunice, Czech Republic
 SOURCE: Ceska a Slovenska Psychiatrie, (2005) Vol. 101, No. 4, pp.
 207-212.
 Refs: 30
 ISSN: 1212-0383 CODEN: CSLPFH
 COUNTRY: Czech Republic
 DOCUMENT TYPE: Journal; Article
 FILE SEGMENT: 030 Pharmacology
 032 Psychiatry
 037 Drug Literature Index
 038 Adverse Reactions Titles
 LANGUAGE: Czech
 SUMMARY LANGUAGE: English; Czech
 ENTRY DATE: Entered STN: 20050707
 Last Updated on STN: 20050707

AB At first a history of development of antidepressants is mentioned.
 Dual-acting antidepressants are a relatively recent class of
 antidepressants. They include both **serotonin** and
norepinephrine reuptake inhibitors (SNRI),
 e.g. venlafaxine, milnacipran and duloxetine and a representative of
 noradrenergic and specific serotonergic antidepressants (NaSSA)
 mirtazapine. Further individual dual-acting antidepressants are compared
 including pharmacological profile, pharmacokinetics, efficacy and side
 effects. In some studies their profile of effectiveness was comparable to
 tricyclics and higher than SSRIs. They are better tolerated than
 tricyclics and similar to SSRIs. They have also a higher rate of
 remissions and according to some studies it seems that they have a faster
 onset of efficacy. Finally new indications of dual-acting antidepressant
 are cited, e.g. anxiety disorders and **pain** including
depression associated pain.

CT Medical Descriptors:
 *depression: DT, drug therapy
 side effect: SI, side effect
 drug efficacy
 drug activity
 drug tolerability

drug potency
remission
drug indication
anxiety disorder: DT, drug therapy
pain: DT, drug therapy
psychopharmacotherapy
anticholinergic effect
nausea: SI, side effect
gastrointestinal symptom: SI, side effect
sedation
insomnia: SI, side effect
sexual dysfunction: SI, side effect
orthostatic hypotension: SI, side effect
human
article

Drug Descriptors:

*antidepressant agent: AE, adverse drug reaction
*antidepressant agent: CM, drug comparison
*antidepressant agent: DO, drug dose
*antidepressant agent: DT, drug therapy
*antidepressant agent: PK, pharmacokinetics
*antidepressant agent: PD, pharmacology
*dual acting antidepressant agent: AE, adverse drug reaction
*dual acting antidepressant agent: CM, drug comparison
*dual acting antidepressant agent: DO, drug dose
*dual acting antidepressant agent: DT, drug therapy
*dual acting antidepressant agent: PK, pharmacokinetics
*dual acting antidepressant agent: PD, pharmacology
serotonin uptake inhibitor: AE, adverse drug reaction
serotonin uptake inhibitor: CM, drug comparison
serotonin uptake inhibitor: DO, drug dose
serotonin uptake inhibitor: DT, drug therapy
serotonin uptake inhibitor: PK, pharmacokinetics
serotonin uptake inhibitor: PD, pharmacology
noradrenalin uptake inhibitor: AE, adverse drug reaction
noradrenalin uptake inhibitor: CM, drug comparison
noradrenalin uptake inhibitor: DO, drug dose
noradrenalin uptake inhibitor: DT, drug therapy
noradrenalin uptake inhibitor: PK, pharmacokinetics
noradrenalin uptake inhibitor: PD, pharmacology
venlafaxine: AE, adverse drug reaction
venlafaxine: DO, drug dose
venlafaxine: DT, drug therapy
venlafaxine: PK, pharmacokinetics
venlafaxine: PD, pharmacology
milnacipran: AE, adverse drug reaction
milnacipran: DO, drug dose
milnacipran: DT, drug therapy
milnacipran: PK, pharmacokinetics
milnacipran: PD, pharmacology
duloxetine: AE, adverse drug reaction
duloxetine: DO, drug dose
duloxetine: DT, drug therapy
duloxetine: PK, pharmacokinetics
duloxetine: PD, pharmacology
mirtazapine: AE, adverse drug reaction
mirtazapine: DO, drug dose
mirtazapine: DT, drug therapy
mirtazapine: PK, pharmacokinetics

mirtazapine: PD, pharmacology
tricyclic antidepressant agent: CM, drug comparison
tricyclic antidepressant agent: DT, drug therapy
monoamine oxidase inhibitor
maprotiline
mianserin
trazodone
amfebutamone
nefazodone
reboxetine
tianeptine
unclassified drug

RN (venlafaxine) 93413-69-5; (milnacipran) 101152-94-7, 86181-08-0,
92623-85-3; (duloxetine) 116539-59-4, 136434-34-9; (mirtazapine)
61337-67-5; (maprotiline) 10262-69-8, 10347-81-6; (mianserin) 21535-47-7,
24219-97-4; (trazodone) 19794-93-5, 25332-39-2; (amfebutamone) 31677-93-7,
34911-55-2; (nefazodone) 82752-99-6, 83366-66-9; (reboxetine) 98769-81-4,
98769-84-7; (tianeptine) 66981-73-5

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ACCESSION NUMBER: 2005162690 EMBASE

TITLE: [Duloxetine: A dual specific **inhibitor** of
serotonin and **norepinephrine**
reuptake in the treatment of acute depressive
disorder].

DULOXETIN - DUALNI SPECIFICKY INHIBITOR REUPTAKE SEROTONINU
A NORADRENALINU V LECBE AKUTNI DEPRESIVNI PORUCHY.

AUTHOR: Svestka J.

CORPORATE SOURCE: Prof. J. Svestka, Psychiatricka Klinika, LF, FN, Jihlavská
20, 639 00 Brno, Czech Republic. jsvestka@med.muni.cz

SOURCE: Psychiatrie, (2005) Vol. 9, No. 1, pp. 23-30.

Refs: 53

ISSN: 1211-7579 CODEN: PCHIF7

COUNTRY: Czech Republic

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 032 Psychiatry
037 Drug Literature Index
038 Adverse Reactions Titles

LANGUAGE: Czech

SUMMARY LANGUAGE: English; Czech

ENTRY DATE: Entered STN: 20050428

Last Updated on STN: 20050428

AB Duloxetine is the most potent serotonin and norepinephrine reuptake
inhibitor in neuronal synapses from the whole group of dual
antidepressants. In 8 double-blind, placebo controlled trials, duloxetine
in the indication of acute depressive disorder had greater therapeutic
effect than placebo and the same effect as fluoxetine and paroxetine in
6/8 of comparisons. The onset of antidepressant and anxiolytic action was
observed after 1-2 weeks of therapy. Duloxetine was also efficient in
reducing **pain** symptoms associated with **depression**.

Other indications of duloxetine include painful diabetic neuropathy and
stress-induced urinary incontinence in women. The most frequent
undesirable effects were nausea, dry mouth, obstipation and insomnia; the
incidence of sexual dysfunction was less frequent than in paroxetine
therapy.

CT Medical Descriptors:

*depression: DT, drug therapy
drug mechanism

drug potency
synapse
tranquilizing activity
dose time effect relation
pain assessment
symptomatology
disease association
diabetic neuropathy
urine incontinence
side effect: SI, side effect
nausea: SI, side effect
xerostomia: SI, side effect
constipation: SI, side effect
insomnia: SI, side effect
sexual dysfunction: SI, side effect
human
major clinical study
clinical trial
randomized controlled trial
double blind procedure
controlled study
article

Drug Descriptors:

*serotonin uptake inhibitor: AE, adverse drug reaction
*serotonin uptake inhibitor: CT, clinical trial
*serotonin uptake inhibitor: CM, drug comparison
*serotonin uptake inhibitor: DT, drug therapy
*noradrenalin uptake inhibitor: AE, adverse drug reaction
*noradrenalin uptake inhibitor: CT, clinical trial
*noradrenalin uptake inhibitor: CM, drug comparison
*noradrenalin uptake inhibitor: DT, drug therapy
*duloxetine: AE, adverse drug reaction
*duloxetine: CT, clinical trial
*duloxetine: CM, drug comparison
*duloxetine: DT, drug therapy
*antidepressant agent: AE, adverse drug reaction
*antidepressant agent: CT, clinical trial
*antidepressant agent: CM, drug comparison
*antidepressant agent: DT, drug therapy
paroxetine: AE, adverse drug reaction
paroxetine: CT, clinical trial
paroxetine: CM, drug comparison
paroxetine: DT, drug therapy
venlafaxine: DT, drug therapy
milnacipran: DT, drug therapy
tricyclic antidepressant agent: DT, drug therapy
imipramine: DT, drug therapy
clomipramine: DT, drug therapy
amitriptyline: DT, drug therapy
fluoxetine: DT, drug therapy
citalopram: DT, drug therapy
fluvoxamine: DT, drug therapy
sertraline: DT, drug therapy
desipramine: DT, drug therapy
nortriptyline: DT, drug therapy
reboxetine: DT, drug therapy
atomoxetine: DT, drug therapy
placebo

RN (duloxetine) 116539-59-4, 136434-34-9; (paroxetine) 61869-08-7;

(venlafaxine) 93413-69-5; (milnacipran) 101152-94-7, 86181-08-0, 92623-85-3; (imipramine) 113-52-0, 50-49-7; (clomipramine) 17321-77-6, 303-49-1; (amitriptyline) 50-48-6, 549-18-8; (fluoxetine) 54910-89-3, 56296-78-7, 59333-67-4; (citalopram) 59729-33-8; (fluvoxamine) 54739-18-3; (sertraline) 79617-96-2; (desipramine) 50-47-5, 58-28-6; (nortriptyline) 72-69-5, 894-71-3; (reboxetine) 98769-81-4, 98769-84-7; (atomoxetine) 82248-59-7, 82857-39-4, 82857-40-7, 83015-26-3

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ACCESSION NUMBER: 2002400175 EMBASE
 TITLE: Chronic **pain** and **depression**.
 AUTHOR: Goli V.; Fozdar M.
 CORPORATE SOURCE: Dr. V. Goli, Pain Evaluation/Treatment Services, Department Psychiatry/Anesthesiology, Durham, NC, United States
 SOURCE: Economics of Neuroscience, (2002) Vol. 4, No. 2, pp. 40-47.
 Refs: 59
 ISSN: 1527-0815 CODEN: ENCEBO
 COUNTRY: United States
 DOCUMENT TYPE: Journal; Article
 FILE SEGMENT: 008 Neurology and Neurosurgery
 030 Pharmacology
 032 Psychiatry
 037 Drug Literature Index
 038 Adverse Reactions Titles
 LANGUAGE: English
 SUMMARY LANGUAGE: English
 ENTRY DATE: Entered STN: 20021121
 Last Updated on STN: 20021121

AB Relief of suffering has been the cornerstone of the medical profession since Hippocratic times. Pain disorders are estimated to cost the American economy \$100 billion annually in health care, lost productivity, workers' compensation, etc. The field of pain medicine has witnessed significant advances on several fronts in the past decade-both in understanding of the causation of pain disorders as well as their treatment. Despite these advances, chronic pain remains a medical enigma. Clinicians have traditionally looked at pain disorders in a dichotomous fashion, physiological versus psychological. This schism leads to treatment approaches that isolate symptoms and treat target organs. On the other hand, psychiatric issues such as depression, personality factors, etc., play a major role in the treatment of a chronic-pain patient. This has been established beyond a reasonable doubt through multiple scientific studies. Depression is the leading psychiatric disorder in patients with chronic-pain syndromes. Identification and treatment of comorbid **pain** and **depression** is a quintessential challenge faced by clinicians at all levels-primary care offices, specialty offices, and pain clinics. One of the reasons for this, in our opinion, is the failure of the current Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition classification system to explain the complex relationship between chronic **pain** and **depression**. To invoke a chicken-or-egg analogy, clinicians are often left wondering, "What came first, **pain** or **depression**?" A thorough understanding of the psychodynamic factors in a particular patient is quite helpful and an essential step towards solving the jigsaw puzzle. Early and effective intervention in comorbid **pain** and **depression** might help prevent the undesired complications of inadequate treatment of both of these chronic conditions. To succeed in this task, a better understanding of the phenomenology and physiology of both the conditions by any clinician involved in taking care

of these patients is absolutely essential. Diagnosing **depression** in chronic **pain** and using a multidisciplinary approach to treatment is advocated.

CT

Medical Descriptors:

*depression: DI, diagnosis
 *depression: DT, drug therapy
 *depression: TH, therapy
 *chronic pain: DT, drug therapy
 *chronic pain: TH, therapy
 comorbidity
 health care cost
 productivity
 workman compensation
 symptomatology
 personality disorder
 primary medical care
 medical specialist
 pain clinic
 disease classification
 psychodynamics
 patient care
 neurophysiology
 neuropsychiatry
 pain assessment
 drug mechanism
 xerostomia: SI, side effect
 orthostatic hypotension
 urine retention: SI, side effect
 heart disease: SI, side effect
 drug potentiation
 tardive dyskinesia: SI, side effect
 extrapyramidal symptom: SI, side effect
 anticholinergic effect
 cognitive defect: SI, side effect
 liver toxicity: SI, side effect
 drug hypersensitivity: SI, side effect
 metabolic disorder: SI, side effect
 endocrine disease: SI, side effect
 immunopathology: SI, side effect
 human
 clinical trial
 controlled study
 article

Drug Descriptors:

tricyclic antidepressant agent: AE, adverse drug reaction
 tricyclic antidepressant agent: CB, drug combination
 tricyclic antidepressant agent: DT, drug therapy
 tricyclic antidepressant agent: PD, pharmacology
 serotonin uptake inhibitor: AE, adverse drug reaction
 serotonin uptake inhibitor: DT, drug therapy
 serotonin uptake inhibitor: PD, pharmacology
 antidepressant agent: AE, adverse drug reaction
 antidepressant agent: CT, clinical trial
 antidepressant agent: CB, drug combination
 antidepressant agent: IT, drug interaction
 antidepressant agent: DT, drug therapy
 antidepressant agent: PD, pharmacology
serotonin norepinephrine reuptake inhibitor: AE, adverse drug reaction

serotonin norepinephrine reuptake inhibitor: DT, drug therapy
serotonin norepinephrine reuptake inhibitor: PD, pharmacology
monoamine oxidase inhibitor: CB, drug combination
monoamine oxidase inhibitor: IT, drug interaction
monoamine oxidase inhibitor: DT, drug therapy
monoamine oxidase inhibitor: PD, pharmacology
amitriptyline: AE, adverse drug reaction
amitriptyline: DT, drug therapy
amitriptyline: PD, pharmacology
desipramine: AE, adverse drug reaction
desipramine: DT, drug therapy
desipramine: PD, pharmacology
fluoxetine: AE, adverse drug reaction
fluoxetine: DT, drug therapy
fluoxetine: PD, pharmacology
paroxetine: AE, adverse drug reaction
paroxetine: DT, drug therapy
paroxetine: PD, pharmacology
phenelzine: CB, drug combination
phenelzine: IT, drug interaction
phenelzine: DT, drug therapy
phenelzine: PD, pharmacology
pethidine: CB, drug combination
pethidine: IT, drug interaction
anesthetic agent: CB, drug combination
anesthetic agent: IT, drug interaction
venlafaxine: CT, clinical trial
venlafaxine: DT, drug therapy
venlafaxine: PD, pharmacology
neuroleptic agent: AE, adverse drug reaction
neuroleptic agent: CB, drug combination
neuroleptic agent: DT, drug therapy
neuroleptic agent: PD, pharmacology
haloperidol: AE, adverse drug reaction
haloperidol: DT, drug therapy
haloperidol: PD, pharmacology
fluphenazine: AE, adverse drug reaction
fluphenazine: CB, drug combination
fluphenazine: DT, drug therapy
fluphenazine: PD, pharmacology
risperidone: AE, adverse drug reaction
risperidone: DT, drug therapy
risperidone: PD, pharmacology
olanzapine: AE, adverse drug reaction
olanzapine: DT, drug therapy
olanzapine: PD, pharmacology
benzodiazepine: DT, drug therapy
benzodiazepine: PD, pharmacology
clonazepam: DT, drug therapy
clonazepam: PD, pharmacology
anticonvulsive agent: AE, adverse drug reaction
anticonvulsive agent: CT, clinical trial
anticonvulsive agent: DT, drug therapy
anticonvulsive agent: PD, pharmacology
lamotrigine: AE, adverse drug reaction
lamotrigine: CT, clinical trial
lamotrigine: DT, drug therapy
lamotrigine: PD, pharmacology
valproate semisodium: AE, adverse drug reaction

valproate semisodium: DT, drug therapy
 valproate semisodium: PD, pharmacology
 gabapentin: AE, adverse drug reaction
 gabapentin: CT, clinical trial
 CT Drug Descriptors:
 gabapentin: DT, drug therapy
 gabapentin: PD, pharmacology
 felbamate: AE, adverse drug reaction
 felbamate: CT, clinical trial
 felbamate: DT, drug therapy
 felbamate: PD, pharmacology
 topiramate: AE, adverse drug reaction
 topiramate: CT, clinical trial
 topiramate: DT, drug therapy
 topiramate: PD, pharmacology
 oxcarbazepine: AE, adverse drug reaction
 oxcarbazepine: CT, clinical trial
 oxcarbazepine: DT, drug therapy
 oxcarbazepine: PD, pharmacology
 carbamazepine: AE, adverse drug reaction
 carbamazepine: DT, drug therapy
 carbamazepine: PD, pharmacology
 phenytoin: AE, adverse drug reaction
 phenytoin: DT, drug therapy
 phenytoin: PD, pharmacology
 unindexed drug
 unclassified drug
 RN (amitriptyline) 50-48-6, 549-18-8; (desipramine) 50-47-5, 58-28-6;
 (fluoxetine) 54910-89-3, 56296-78-7, 59333-67-4; (paroxetine) 61869-08-7;
 (phenelzine) 156-51-4, 51-71-8; (pethidine) 28097-96-3, 50-13-5, 57-42-1;
 (venlafaxine) 93413-69-5; (haloperidol) 52-86-8; (fluphenazine) 146-56-5,
 69-23-8; (risperidone) 106266-06-2; (olanzapine) 132539-06-1;
 (benzodiazepine) 12794-10-4; (clonazepam) 1622-61-3; (lamotrigine)
 84057-84-1; (valproate semisodium) 76584-70-8; (gabapentin) 60142-96-3;
 (felbamate) 25451-15-4; (topiramate) 97240-79-4; (oxcarbazepine)
 28721-07-5; (carbamazepine) 298-46-4, 8047-84-5; (phenytoin) 57-41-0,
 630-93-3

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ACCESSION NUMBER: 97018155 EMBASE
 DOCUMENT NUMBER: 1997018155
 TITLE: Depression in the patient with chronic pain.
 AUTHOR: Ruoff G.E.; De Wester J.N.; Richardson F.; Susman J.L.
 CORPORATE SOURCE: Dr. G.E. Ruoff, 6565 West Main, Kalamazoo, MI 49009, United States
 SOURCE: Journal of Family Practice, (1996) Vol. 43, No. 6 SUPPL., pp. S25-S34.
 Refs: 53
 ISSN: 0094-3509 CODEN: JFAPDE
 COUNTRY: United States
 DOCUMENT TYPE: Journal; Article
 FILE SEGMENT: 032 Psychiatry
 037 Drug Literature Index
 038 Adverse Reactions Titles
 LANGUAGE: English
 SUMMARY LANGUAGE: English
 ENTRY DATE: Entered STN: 970215
 Last Updated on STN: 970215

AB The management of patients with chronic pain is a challenging clinical problem that frequently requires a multidisciplinary approach. Depression is a common comorbidity associated with chronic pain, occurring in as many as 50% of chronic pain patients. **Depression** may develop **secondarily** or independently of the chronic pain syndrome, or it may occur as the primary cause of chronic pain. Regardless of their etiology, evidence exists to suggest that depression and chronic pain share common biologic pathways, namely, the serotonergic (5-HT) and noradrenergic systems. Chronic pain patients who are depressed require aggressive, full-dose treatment with antidepressants. Treatment should be selected based on a prior clinical response, the side-effect profile, the dosing schedule, and the potential for drug interactions. The newer antidepressants, including the selective serotonin reuptake inhibitors venlafaxine and nefazodone, are therapeutic options for the treatment of depression in the patient with chronic pain.

CT Medical Descriptors:

- *chronic pain
- *depression: CO, complication
- *depression: DT, drug therapy
- article
- differential diagnosis
- disease association
- drug choice
- drug contraindication
- drug efficacy
- heart ventricle arrhythmia: SI, side effect
- human
- nociception
- noradrenergic system
- orthostatic hypotension: SI, side effect
- pathophysiology
- priapism: SI, side effect
- serotonergic system
- suicidal behavior: CO, complication
- treatment planning
- vertigo: SI, side effect
- visual impairment: SI, side effect
- Drug Descriptors:
 - *monoamine oxidase inhibitor: AE, adverse drug reaction
 - *monoamine oxidase inhibitor: IT, drug interaction
 - *monoamine oxidase inhibitor: CM, drug comparison
 - *monoamine oxidase inhibitor: DO, drug dose
 - *serotonin uptake inhibitor: CM, drug comparison
 - *serotonin uptake inhibitor: AE, adverse drug reaction
 - *serotonin uptake inhibitor: DO, drug dose
 - *serotonin uptake inhibitor: IT, drug interaction
 - *serotonin uptake inhibitor: DT, drug therapy
 - *tricyclic antidepressant agent: DT, drug therapy
 - *tricyclic antidepressant agent: DO, drug dose
 - *tricyclic antidepressant agent: CM, drug comparison
 - *tricyclic antidepressant agent: AE, adverse drug reaction
- amfebutamone: IT, drug interaction
- amfebutamone: DT, drug therapy
- amfebutamone: AE, adverse drug reaction
- amfebutamone: CM, drug comparison
- amfebutamone: DO, drug dose
- amitriptyline: AE, adverse drug reaction
- amitriptyline: DT, drug therapy
- amitriptyline: DO, drug dose

amitriptyline: CM, drug comparison
amitriptyline: IT, drug interaction
desipramine: DT, drug therapy
desipramine: IT, drug interaction
desipramine: DO, drug dose
desipramine: CM, drug comparison
desipramine: AE, adverse drug reaction
fluoxetine: AE, adverse drug reaction
fluoxetine: CM, drug comparison
fluoxetine: DO, drug dose
fluoxetine: IT, drug interaction
fluoxetine: PD, pharmacology
fluvoxamine: DT, drug therapy
fluvoxamine: DO, drug dose
fluvoxamine: PD, pharmacology
fluvoxamine: IT, drug interaction
fluvoxamine: CM, drug comparison
fluvoxamine: AE, adverse drug reaction
nefazodone: PD, pharmacology
nefazodone: DT, drug therapy
nefazodone: IT, drug interaction
nefazodone: AE, adverse drug reaction
nefazodone: CM, drug comparison
nefazodone: DO, drug dose
nortriptyline: CM, drug comparison
nortriptyline: AE, adverse drug reaction
nortriptyline: DT, drug therapy
nortriptyline: DO, drug dose
nortriptyline: IT, drug interaction
paroxetine: AE, adverse drug reaction
paroxetine: CM, drug comparison
paroxetine: DO, drug dose
paroxetine: IT, drug interaction
paroxetine: DT, drug therapy
phenelzine: CM, drug comparison
phenelzine: AE, adverse drug reaction
phenelzine: DO, drug dose
phenelzine: IT, drug interaction
phenelzine: DT, drug therapy
sertraline: CM, drug comparison
sertraline: DO, drug dose
sertraline: AE, adverse drug reaction
sertraline: IT, drug interaction
sertraline: DT, drug therapy
tranylcypromine: IT, drug interaction
tranylcypromine: CM, drug comparison
tranylcypromine: DO, drug dose
tranylcypromine: DT, drug therapy
tranylcypromine: AE, adverse drug reaction
trazodone: IT, drug interaction
trazodone: DT, drug therapy
trazodone: AE, adverse drug reaction
trazodone: CM, drug comparison
trazodone: DO, drug dose
venlafaxine: CM, drug comparison
venlafaxine: DO, drug dose
venlafaxine: IT, drug interaction
venlafaxine: DT, drug therapy
venlafaxine: AE, adverse drug reaction

RN (amfebutamone) 31677-93-7, 34911-55-2; (amitriptyline) 50-48-6, 549-18-8; (desipramine) 50-47-5, 58-28-6; (fluoxetine) 54910-89-3, 56296-78-7, 59333-67-4; (fluvoxamine) 54739-18-3; (nefazodone) 82752-99-6, 83366-66-9; (nortriptyline) 72-69-5, 894-71-3; (paroxetine) 61869-08-7; (phenelzine) 156-51-4, 51-71-8; (sertraline) 79617-96-2; (tranylcypromine) 13492-01-8, 155-09-9, 54-97-7; (trazodone) 19794-93-5, 25332-39-2; (venlafaxine) 93413-69-5

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ACCESSION NUMBER: 92178858 EMBASE
DOCUMENT NUMBER: 1992178858
TITLE: 'Newer' versus 'older' antidepressant drugs in the treatment of chronic pain syndromes.
AUTHOR: De Angelis L.
CORPORATE SOURCE: Institute of Pharmacology, University of Trieste, Via A. Valerio, 32, 34127 Trieste, Italy
SOURCE: Advances in Therapy, (1992) Vol. 9, No. 2, pp. 91-97.
ISSN: 0741-238X CODEN: ADTHE7
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 008 Neurology and Neurosurgery
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 920705
Last Updated on STN: 920705

AB A substantial body of data documents the efficacy of **antidepressant** drugs in chronic **pain** syndromes. In this paper, we discuss the mechanism of the analgesic action of antidepressants and review the available data on newer antidepressants (**norepinephrine reuptake inhibitors**, **serotonin reuptake inhibitors** and agonists, **nonreuptake inhibitors**) in the treatment of chronic pain syndromes.

CT Medical Descriptors:
*analgesia
*chronic pain: DT, drug therapy
calcium channel
drug efficacy
drug mechanism
drug potency
gastrointestinal symptom: SI, side effect
human
review
serotoninergetic system
xerostomia: SI, side effect
Drug Descriptors:
*antidepressant agent: DT, drug therapy
*antidepressant agent: PD, pharmacology
*serotonin uptake inhibitor: PD, pharmacology
*serotonin uptake inhibitor: DT, drug therapy
amitriptyline: DT, drug therapy
amitriptyline: PD, pharmacology
clomipramine: DT, drug therapy
clomipramine: PD, pharmacology
endorphin: EC, endogenous compound
fluoxetine: PD, pharmacology

fluoxetine: DT, drug therapy
 imipramine: PD, pharmacology
 imipramine: DT, drug therapy
 maprotiline: PD, pharmacology
 maprotiline: DT, drug therapy
 maprotiline: AE, adverse drug reaction
 mianserin: DT, drug therapy
 mianserin: PD, pharmacology
 paroxetine: PD, pharmacology
 paroxetine: DT, drug therapy
 serotonin: EC, endogenous compound
 trazodone: DT, drug therapy
 trazodone: PD, pharmacology
 zimeldine: AE, adverse drug reaction
 zimeldine: DT, drug therapy
 zimeldine: PD, pharmacology

RN (amitriptyline) 50-48-6, 549-18-8; (clomipramine) 17321-77-6, 303-49-1;
 (endorphin) 60118-07-2; (fluoxetine) 54910-89-3, 56296-78-7, 59333-67-4;
 (imipramine) 113-52-0, 50-49-7; (maprotiline) 10262-69-8, 10347-81-6;
 (mianserin) 21535-47-7, 24219-97-4; (paroxetine) 61869-08-7; (serotonin)
 50-67-9; (trazodone) 19794-93-5, 25332-39-2; (zimeldine) 56775-88-3,
 60525-15-7

L91 ANSWER 288 OF 313 EMBASE COPYRIGHT (c) 2005 Elsevier B.V. All rights
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ACCESSION NUMBER: 90177634 EMBASE
 DOCUMENT NUMBER: 1990177634
 TITLE: Painful peripheral neuropathies: Mechanisms and treatment.
 AUTHOR: Dubner R.; Max M.B.
 CORPORATE SOURCE: Neurobiology and Anesthesiology Branch, National Institute
 of Dental Research, National Institutes of Health,
 Bethesda, MD 20892, United States
 SOURCE: Serotonin and pain: proceedings of the International
 Symposium on Serotonin and pain. ICS879, (1990)
 (327-338+336).
 Conference: The International Symposium on Serotonin and
 pain, La Roque-Gageac, FRANCE, 17 SEP 1989 - 21 SEP 1989
 Editor: Besson J.-M. Publisher: Elsevier Science
 Publishers B.V.
 ISBN: 044481115X
 DOCUMENT TYPE: Conference; Conference Article
 FILE SEGMENT: 008 Neurology and Neurosurgery
 037 Drug Literature Index
 LANGUAGE: English
 SUMMARY LANGUAGE: English
 ENTRY DATE: Entered STN: 911213
 Last Updated on STN: 911213

AB Painful peripheral neuropathies are among the most difficult chronic pain
 problems to treat. Recent studies in the peripheral and central nervous
 system indicate that there are multiple underlying mechanisms of
 neuropathic pain. A number of pathological changes take place in the
 peripheral nervous system following nerve injury and appear to be
 important for the painful conditions to occur. When a nerve is damaged,
 axons sprout from the site of injury and form a neuroma. The new nerve
 sprout emit spontaneous discharges and are responsive to mechanical,
 thermal and chemical stimulation. Ectopic discharges can also arise from
 the cell body of primary afferent neurons with consequences similar to
 spontaneous activity arising from neuromas. Another mechanism of
 pathological transmission in damaged nerve is cross-excitation from one

nerve fiber to another. Such a mechanism can lead to activation of damaged nociceptive fibers via cross-excitation with intact mechanoreceptive afferents. Following peripheral nerve injury, there also is an alteration in the receptive field organization of nociceptive neurons in the medullary and spinal dorsal horns. Peripheral deafferentation leads to an expansion of the receptive fields of these neurons that is likely related to a loss of inhibitory mechanisms in the dorsal horn. The expanded receptive fields will lead to a greater number of nociceptive neurons activated by the stimulus which may ultimately be perceived as more intense pain. Thus, we can postulate that peripheral nerve injury results in ectopic discharges which ultimately results in a loss of central inhibition, expanded receptive fields of central nociceptive neurons, hyperexcitability and increased perceived pain. The pathophysiology involves alterations in both peripheral and central nervous system mechanisms related to the processing of nociceptive information. Therapies that reverse this loss of central inhibition are effective analgesic agents in the treatment of painful neuropathies. This includes anticonvulsive agents such as carbamazepine and phenytoin. Recent studies have shown that tricyclic antidepressants are effective analgesic agents for painful neuropathies. Their efficacy is independent of the drugs' effects on mood. Their mechanism of action is linked to the blockage of the synaptic reuptake of serotonin or norepinephrine, putative inhibitory chemical mediators in the dorsal horn. All effective tricyclic antidepressants evaluated under control conditions block norepinephrine reuptake or have active metabolites that do so. The findings suggest that serotonergic mechanisms may not be essential for the analgesic effects of tricyclic antidepressants.

CT Medical Descriptors:

*neuralgia
 *neuropathy
 *pain: DT, drug therapy
 cat
 noradrenergic system
 serotonergic system
 major clinical study
 animal experiment
 human
 nonhuman
 conference paper

Drug Descriptors:

*antidepressant agent: PD, pharmacology
 *antidepressant agent: DT, drug therapy
 *antidepressant agent: CM, drug comparison
 amitriptyline
 desipramine
 lorazepam

RN (amitriptyline) 50-48-6, 549-18-8; (desipramine) 50-47-5, 58-28-6;
 (lorazepam) 846-49-1

L91 ANSWER 289 OF 313 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN

ACCESSION NUMBER: 2005-630311 [64] WPIX

CROSS REFERENCE: 2005-571344 [58]

DOC. NO. CPI: C2005-189063

TITLE: Composition, useful to treat e.g. epilepsy, seizure disorder, **depression, pain**, neuropathies, cerebroischemia and dementias, comprises a N-methyl D-aspartate receptor antagonist and an anti-depressive drug.

DERWENT CLASS: B05
 INVENTOR(S): FULTZ, T J; MEYERSON, L; WENT, G
 PATENT ASSIGNEE(S): (NEUR-N) NEUROMOLECULAR INC
 COUNTRY COUNT: 108
 PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2005079756	A2	20050901	(200564)*	EN	38
RW: AT BE BG BW CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IS IT KE LS LT LU MC MW MZ NA NL OA PL PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW					
W: AE AG AL AM AT AU AZ BA BB BG BR BW BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NA NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW					

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2005079756	A2	WO 2005-US4917	20050214

PRIORITY APPLN. INFO: US 2004-544838P 20040213

AB WO2005079756 A UPAB: 20051006

NOVELTY - Composition (A) comprises an N-methyl D-aspartate (NMDA) receptor antagonist (I); a second agent (II) (an anti-depressive drug (ADD)); and a carrier (III), where (I) or (II) is provided in an extended release dosage form.

ACTIVITY - CNS-Gen.; Anticonvulsant; Analgesic; Neuroleptic; Antidepressant; Tranquilizer; Nootropic; Neuroprotective; Antiparkinsonian; Cerebroprotective; Auditory; Muscular-Gen.; Antianginal; Antiinflammatory; Antileprotic; Antidote; Antiaddictive; Immunomodulator.

MECHANISM OF ACTION - N-Methyl D-aspartate receptor antagonist.

No biological data given.

USE - (A) is useful to treat CNS-related condition (epilepsy, seizure disorder, chronic nociceptive pain or convulsive disorder) (claimed). (A) is also useful to treat e.g. psychiatric conditions such as depression (major, refractory and bipolar), degeneration associated with **depression**, anxiety headache, **pain**, neuropathies, cereborischemia, dementias, movement disorders, multiple sclerosis, Parkinson's disease, picks disease, fronto-temporal dementia, vascular dementia, Wilson's disease, trigeminal neuropathy, trigeminal neuralgia, Menier's syndrome, ataxic syndromes, disorders of sympathetic nervous system, post-menengitis syndrome, prion diseases, myelitides, radiculitis, neuropathies, carpal tunnel syndrome, tarsal tunnel syndrome, amyloid-induced neuropathies, leprous neuropathy, Bell's palsy, compression neuropathies, sarcoidosis-induced neuropathy, polyneuritis cranialis, heavy metal induced neuropathy, transition metal-induced neuropathy, drug-induced neuropathy, pain syndromes, axonic brain damage, encephalopathies, and chronic fatigue syndrome.

Dwg.0/4

L91 ANSWER 290 OF 313 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN

ACCESSION NUMBER: 2005-356061 [36] WPIX

DOC. NO. CPI: C2005-110148

TITLE: New triazolo-pyridazine derivatives are alpha-2-delta

subunit calcium channel binders useful to treat/prevent
e.g. neuropathic pain, anxiety disorders,
depression, bipolar disorders, memory loss,
Alzheimer's disease and panic disorder.

DERWENT CLASS: B02
INVENTOR(S): GUNZNER, J; LEBSACK, A D; MUNOZ, B; PRACITTO, R;
VENKATRAMAN, S; WANG, B
PATENT ASSIGNEE(S): (MERI) MERCK & CO INC
COUNTRY COUNT: 108
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2005041971	A1	20050512	(200536)*	EN	119
RW: AT BE BG BW CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS LU MC MW MZ NA NL OA PL PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW					
W: AE AG AL AM AT AU AZ BA BB BG BR BW BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NA NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW					

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2005041971	A1	WO 2004-US34466	20041015

PRIORITY APPLN. INFO: US 2003-513046P 20031021

AB WO2005041971 A UPAB: 20050608

NOVELTY - Triazolo-pyridazine derivatives (A1) and their salts are new.
DETAILED DESCRIPTION - Triazolo-pyridazine derivatives (A1) of
formula (I or II) and their salts are new.

A, B1 = CH₂, N or O;

D, E = N or O;

F1 = phenyl or heteroaryl (pyridyl);

G = methylene (optionally substituted with a substituent of CH₃,
ethyl, isopropyl or carbonyl) or a bond;

R = H, CF₃ or CH₃;

R1 = H, CF₃, phenyl, 1-6C alkyl, 3-6C cycloalkyl, 2-6C alkenyl, 2-6C
alkynyl, O-1-6C alkyl, -O-2-6C alkenyl, S-1-6C alkyl or a heteroaromatic
ring of 5-6 members (where the heteroaromatic ring comprises 1-3
heteroatoms of N or O) (where the heteroaryl is optionally substituted
with CH₃, OCH₃, hydroxyl or halo); either

R2, R3 = H, 1-6C alkyl, heteroaromatic ring of 5-6 members (where
the heterocycloalkyl or heteroaromatic ring comprises 1-3 heteroatoms of N
or O), aryl or NR₅R₆ (all optionally substituted with 1-2 substituents of
CH₃, OCH₃, halo or hydroxyl); or

R2+R3 = a ring of phenyl or cyclohexyl;

R4 = NH(1-3C alkylaryl) (optionally substituted with 1-2
substituents of halo, hydroxyl, 1-6C alkyl or O-1-6C alkyl); and

R7 = N(CH₃)₂, aryl, a heteroaromatic ring of 5-6 members (where the
heteroaromatic ring comprises 1-3 heteroatoms of N or O) (all optionally
substituted with CH₃, OCH₃, hydroxyl or halo) or hydroxyl.

An INDEPENDENT CLAIM is also included for a composition (A2), for
treating an indication mediated by the binding of an alpha 2 delta subunit
of voltage gated calcium channel, comprising (I) or their salts and
carriers.

ACTIVITY - Analgesic; Tranquilizer; Eating-Disorders-Gen.; Antidepressant; Neuroleptic; Antiaddictive; Antismoking; Nootropic; Neuroprotective; Anticonvulsant; Antiparkinsonian; Antiinflammatory; CNS-Gen.; Hypnotic.

MECHANISM OF ACTION - Alpha-2-delta subunit calcium channel binder; Gabapentin binder.

The ability of (I) to bind with gabapentin was tested using an in vitro assay. The results showed that (I) exhibited a median inhibitory concentration value of 10 micro M.

USE - (A1) are useful for the treatment or prevention of neuropathic pain, pain disorders (acute pain, persistent pain, chronic pain or inflammatory pain), anxiety disorders (panic attack, agoraphobia, specific phobias, obsessive-compulsive disorders, post-traumatic stress disorder, acute stress disorder, eating disorder, substance-induced anxiety disorder or nonspecified anxiety disorder), depression, bipolar disorders, psychosis, drug withdrawal, tobacco withdrawal, memory loss, cognitive impairment, dementia, Alzheimer's disease, schizophrenia, extrapyramidal motor function disorders (progressive supramuscular palsy, Huntington's disease, Gilles de la Tourette syndrome or tardive dyskinesia), Parkinson's disease, epilepsy, inflammatory pain, cognitive dysfunction, drug addiction/abuse, circadian rhythm and sleep disorders (shift-work induced sleep disorder or jet-lag) (all claimed). (A1) are also useful for the treatment psychiatric and mood disorders.

ADVANTAGE - (I) having control isoform are likely to be more efficacious and display fewer side-effects.

Dwg.0/0

L91 ANSWER 291 OF 313 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
 ACCESSION NUMBER: 2005-322782 [33] WPIX
 DOC. NO. CPI: C2005-100658
 TITLE: New fused-aryl and heteroaryl derivatives, useful for treatment or prevention of condition ameliorated by monoamine reuptake in a subject e.g. sexual or gastrointestinal dysfunction, **pain**, nervous system disorders and **depression**.
 DERWENT CLASS: B02 B03
 INVENTOR(S): GAVRIN, L K; MAHANEY, P E; SABATUCCI, J P; STACK, G P; TRYBULSKI, E J; KRIM, L D
 PATENT ASSIGNEE(S): (AMHP) WYETH
 COUNTRY COUNT: 108
 PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2005037283	A1	20050428	(200533)*	EN	334
RW: AT BE BG BW CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE					
LS LU MC MW MZ NA NL OA PL PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW					
W: AE AG AL AM AT AU AZ BA BB BG BR BW BY BZ CA CH CN CO CR CU CZ DE					
DK DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG					
KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NA NI NO NZ					
OM PG PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG					
US UZ VC VN YU ZA ZM ZW					
US 2005192283	A1	20050901	(200558)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2005037283	A1	WO 2004-US33671	20041013

US 2005192283	A1 Provisional	US 2003-510811P	20031014
	Provisional	US 2004-561447P	20040412
	Provisional	US 2004-570056P	20040511
		US 2004-963064	20041012

PRIORITY APPLN. INFO: US 2004-963064 20041012; US
 2003-510811P 20031014; US
 2004-561447P 20040412; US
 2004-570056P 20040511

AB WO2005037283 A UPAB: 20050524

NOVELTY - Fused-aryl and heteroaryl derivatives (I) are new.

DETAILED DESCRIPTION - Fused-aryl and heteroaryl derivatives of formula (I) and their salts are new.

A = naphthyl, thiophenyl, pyridinyl, furanyl, benzofuranyl, isobenzofuranyl, xanthenyl, pyrrolyl, indolizinyll, isoindolyl, indolyl or benzothiophenyl (where 1-3 carbon atoms are optionally replaced by nitrogen and/or all optionally substituted by at least one R1);

W = H or OR9;

R1 = benzyloxy, phenyloxy, naphthyloxy, phenyl, heteroaryl, heteroaryloxy or heteroarylmethoxy (all optionally substituted by at least one R1), H, OH, alkyl, alkoxy, halo, trifluoromethyl, alkanoyloxy, methylenedioxy, nitro, trifluoromethoxy, nitrile, alkenyl, alkynyl, sulfoxide, sulfonyl, sulfonamido, alkanoyl, alkoxycarbonyl, alkylaminocarbonyl or amino;

R5 = H, 1-6C alkyl or trifluoromethyl;

R6, R7 = 1-6C alkyl or 3-6C cycloalkyl where any carbon atom is optionally replaced by N, S or O (both optionally substituted by R5 or OH); or

R6+R7 = 4-8 membered ring (optionally fused onto 4-6 membered cycloalkyl ring);

R8 = T1 or H;

T1 = benzyl (optionally substituted by benzyloxy or phenyloxy), naphthylmethyl, phenyl(2-6C alkyl) or heteroarylmethyl (all optionally substituted by at least one R1), cycloalkylmethyl or cycloalkenylmethyl (where any carbon atom is optionally replaced by N, S or O and/or both optionally substituted by OH, CF3, halo, alkoxy, alkyl, benzyloxy or alkanolyloxy), cycloalkyl, cycloalkenyl or 1-6C alkyl; or

NR5R8 = ring (optionally substituted by R5);

R9 = H, 1-6C alkyl or C(O)-1-4C alkyl;

t = 1-3; and

x = 0-2.

An INDEPENDENT CLAIM is included for preparation of (I).

ACTIVITY - Gynecological; Antipyretic; Endocrine-Gen.; Gastrointestinal-Gen.; Tranquilizer; Antiinflammatory; Uropathic; Muscular-Gen.; Immunomodulator; CNS-Gen.; Analgesic; Antidiabetic; Neuroprotective; Antidepressant; Hypnotic; Neuroleptic; Antiallergic; Immunosuppressive; Nootropic; Antiaddictive; Antialcoholic; Antismoking; Anabolic; Eating-Disorder-Gen.; Antimigraine; Virucide; Vulnerary; Anorectic.

MECHANISM OF ACTION - **Serotonin reuptake activity inhibitor; Norepinephrine reuptake activity inhibitor; 5-Hydroxytryptamine (5-HT) receptor inhibitor** (preferably 5-HT-2a receptor inhibitor); Selective norepinephrine reuptake inhibitor.

MDCK-Net6 cells stably transfected with human hNET were plated at 3000 cells/well in growth medium and maintained at 37 deg. C and 5% CO2. On day 2, growth medium was replaced with assay buffer containing ascorbic acid (0.2 mg/ml) and pargyline (10 micro M) (200 micro l) and plates

equilibrated for 10 minutes at 37 deg. C. A stock solution of desipramine was prepared in dimethylsulfoxide (DMSO, 10 mM) and delivered to triplicate wells containing cells for a final test concentration of 1 micro M (controls for non-specific NE uptake). 1-(1-(2-Naphthyl)-2-piperazin-1-ylethyl)cyclobutanol dihydrochloride (test compound) was prepared in DMSO (10 mM) and diluted in assay buffer according to test range (1-10000 nM). 25 micro l Assay buffer (maximum NE uptake) or test compound was added directly to triplicate wells containing cells in assay buffer and incubated for 20 minutes at 37 deg. C. To initiate NE uptake, (3H)NE diluted in assay buffer (120 nM final assay concentration) was delivered in aliquots (25 micro l) to each well and the plates incubated for 5 minutes at 37 deg. C. The reaction was terminated by decanting the supernatant from the plate and the plates washed twice with assay buffer (200 micro l) to remove free radioligand. The plates were then inverted, left to dry for 2 minutes, re-inverted and air-dried for an additional 10 minutes. The cells were lyzed at 4 deg. C in 0.25 N NaOH solution (25 micro l) and vigorously shaken for 5 minutes. The test compound showed norepinephrine reuptake inhibition of 97%.

USE - For the treatment or prevention of a condition ameliorated by monoamine reuptake e.g. vasomotor symptoms (e.g. hot flush), sexual dysfunction (e.g. desire-related or arousal-related dysfunction), gastrointestinal and genitourinary disorders (e.g. stress and urge urinary incontinence), chronic fatigue syndrome, fibromyalgia, nervous system disorders, **pain**, diabetic neuropathy, **depression** disorder (e.g. major depressive disorder, anxiety, sleep disturbance or social phobia) in a subject (e.g. human such as pre-menopausal, peri-menopausal or post-menopausal female or naturally, chemically or surgically andropausal) (all claimed). The vasomotor symptoms include insomnia, sleep disturbances, mood disorders, irritability, excessive perspiration, night sweats or fatigue. Gastrointestinal and genitourinary disorder includes irritable bowel syndrome, symptomatic GERD, hypersensitive, esophagus, nonulcer dyspepsia, non-cardiac chest pain, biliary dyskinesia, spincter of Oddi dysfunction, incontinence, interstitial cystitis (irritable bladder) and chronic pelvic pain including vulvodynia, prostatodynia and proctalgia. Chronic fatigue syndrome includes weakness, muscle aches, and pains, excessive sleep, malaise, fever, sore throat, tender lymph nodes, impaired memory and mental concentration, insomnia, disordered sleep, localized tenderness, diffuse pain and fatigue. Fibromyalgia syndrome (FMS) includes FMS and other somatoform disorders, including FMS associated with **depression**, somatization disorder, conversion disorder, **pain** disorder, hypochondriasis, body dysmorphic disorder, undifferentiated somatoform disorder and somatoform NOS. The nervous system disorder includes addictive disorders (including those due to alcohol, nicotine, and other psychoactive substances), withdrawal syndrome, age-associated learning and mental disorders e.g. Alzheimer's disease, anorexia nervosa, bulimia nervosa, attention-deficit disorder with or without hyperactivity disorder, bipolar disorder, pain (including chronic pain e.g. lower back pain, atypical chest pain, migraine, herpes neuralgia, bone injury pain, pain during labor and delivery, pain resulting from burns, postpartum pain, angina pain, neuropathic pain and post-operative **pain**), cyclothymic disorder, **depression** disorder, dysthymic disorder, generalized anxiety disorder, obesity, obsessive compulsive and related spectrum disorders, oppositional defiant disorder, panic disorder, post-traumatic stress disorder, premenstrual dysphoric disorder (i.e. premenstrual syndrome and late luteal phase dysphoric disorder), psychotic disorders including schizophrenia, schizoaffective and schizophreniform disorders, seasonal affective disorder, sleep disorders such as narcolepsy and enuresis, social phobia

(including social anxiety disorder) and selective serotonin reuptake inhibition (SSRI) 'poop out' syndrome.

ADVANTAGE - (I) can adjust dosage regimen to provide therapeutic response. (I) inhibits, suppresses, represses, or decreases serotonin reuptake activity or norepinephrine reuptake activity.

Dwg.0/2

L91 ANSWER 292 OF 313 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
 ACCESSION NUMBER: 2005-322751 [33] WPIX
 DOC. NO. CPI: C2005-100627
 TITLE: New alkanol and cycloalkanol-amine derivatives, useful to treat/prevent e.g. **depression** disorder, sexual dysfunction, **pain**, nervous system disorders and chronic fatigue syndrome, are **norepinephrine** and **serotonin reuptake inhibitors**.
 DERWENT CLASS: B03
 INVENTOR(S): GAVRIN, L K; MAHANEY, P E; MOORE, W J; SABATUCCI, J P; TRYBULSKI, E J; KRIM, L D
 PATENT ASSIGNEE(S): (AMHP) WYETH
 COUNTRY COUNT: 108
 PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2005037207	A2	20050428	(200533)*	EN	355
RW: AT BE BG BW CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS LU MC MW MZ NA NL OA PL PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW W: AE AG AL AM AT AU AZ BA BB BG BR BW BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NA NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW					
US 2005171115	A1	20050804	(200552)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2005037207	A2	WO 2004-US33730	20041013
US 2005171115	A1	Provisional	US 2003-510942P
		Provisional	US 2004-561422P
		Provisional	US 2004-569884P
			US 2004-962880
			20041012

PRIORITY APPLN. INFO: US 2004-962880 20041012; US
 2003-510942P 20031014; US
 2004-561422P 20040412; US
 2004-569884P 20040511

AB WO2005037207 A UPAB: 20050524

NOVELTY - Alkanol and cycloalkanol-amine derivatives (I) are new.

DETAILED DESCRIPTION - Alkanol and cycloalkanol-amine derivatives of formula (I) and their salts are new.

W1 = H or OR9;

R1, R2 = H, OH, alkyl, alkoxy, halo, CF3 or alkanoyloxy; or

R1+R2 = methylene or methylenedioxy;

R5 = H or 1-6C alkyl;

R6, R7 = 1-6C alkyl or 3-6C cycloalkyl; or

CR6R7 = 4-8C ring where any ring C atom is optionally replaced with N, S or O (optionally substituted by 1-4 1-6C alkyl, OH, halo or CF₃ and/or optionally fused to a carbocyclic ring or aromatic ring of 5-8 C atoms or (where 1-2 C atoms of the fused ring may be optionally replaced with N, O or S and where the fused ring is optionally substituted by 1-4 1-6C alkyl, OH, halo or CF₃));

R8 = H or 1-6C alkyl; or

NR5R8 = heterocyclic ring (optionally substituted by 1-4 1-6C alkyl, OH, halo or CF₃);

R9 = H, 1-4C alkyl or C(O)-1-4C alkyl;

t = 1-3; and

x = 0-2.

An INDEPENDENT CLAIM is also included for the preparation of (I).

ACTIVITY - Antidepressant; Tranquilizer; Hypnotic; Endocrine-Gen.; Analgesic; Gastrointestinal-Gen.; Uropathic; Muscular-Gen.; Immunomodulator; Neuroprotective; Antidiabetic; Osteopathic; Antimigraine; Antimicrobial; Gynecological; Contraceptive.

MECHANISM OF ACTION - **Norepinephrine (NE) reuptake inhibitor; Serotonin reuptake inhibitor.**

(I) were tested for their NE reuptake inhibitory activity using NE uptake assay. The results showed that the median effective concentration of 1-(1-(3-chlorophenyl)-2-piperazin-1-ylethyl)cyclohexanol dihydrochloride was 18 nM.

USE - (I) are useful to treat or prevent conditions ameliorated by monoamine reuptake; particularly depression disorder (major depressive disorder, anxiety, sleep disturbance or social phobia), sexual dysfunction (desire-related or arousal-related), pain, gastrointestinal or genitourinary disorder (stress incontinence or urge urinary incontinence), chronic fatigue syndrome, fibromyalgia syndrome in a subject (humans), vasomotor symptoms (hot flush) in a subject (preferably in a pre-, peri- or post-menopausal female or in a naturally, chemically or surgically andropausal male), nervous system disorders, stress and diabetic neuropathy (claimed). (I) are useful to treat chronic pain (e.g. neuropathic pain), cancer pain, bony pain associated with bone or joint degenerating disorders (e.g. osteoarthritis, rheumatoid arthritis or spinal stenosis), headaches (e.g. migraine or tension headaches) or pain associated with infections such as HIV, sickle cell anemia, autoimmune disorders, multiple sclerosis or inflammation (osteoarthritis or rheumatoid arthritis). (I) are useful to treat visceral pain associated with e.g. ulcerative colitis, irritable bowel syndrome, irritable bladder, Crohn's disease, rheumatologic (arthralgias), tumors, gastritis, pancreatitis, infections of the organs or biliary tract disorders) and acute and/or chronic pains associated with female conditions (pain associated with e.g. menstruation, ovulation, pregnancy or childbirth).

ADVANTAGE - (I) are potent **norepinephrine and serotonin reuptake inhibitors** and may be used in treatment of patients where use of steroids is contraindicated.
Dwg.0/2

L91 ANSWER 293 OF 313 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN

ACCESSION NUMBER: 2005-202584 [21] WPIX

CROSS REFERENCE: 2005-202583 [21]

DOC. NO. CPI: C2005-064867

TITLE: New 4-cycloalkyl amino pyrazolo pyrimidine compounds are NMDA/NR2B antagonists, useful for treating and preventing pain, Parkinson's disease, Alzheimer's disease, epilepsy, depression, anxiety and ischemic brain injury.

DERWENT CLASS: B02

INVENTOR(S): BUTCHER, J; DIECKHAUS, C; LIVERTON, N; MCCAULEY, J A;
 MCINTYRE, C J; MUNSON, P; PHILLIPS, B T; THOMPSON, W;
 WHITTER, W; YOUNG, S D
 PATENT ASSIGNEE(S): (MERI) MERCK & CO INC
 COUNTRY COUNT: 108
 PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2005019222	A1	20050303	(200521)*	EN	59
RW: AT BE BG BW CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE					
LS LU MC MW MZ NA NL OA PL PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW					
W: AE AG AL AM AT AU AZ BA BB BG BR BW BY BZ CA CH CN CO CR CU CZ DE					
DK DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG					
KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NA NI NO NZ					
OM PG PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG					
US UZ VC VN YU ZA ZM ZW					

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2005019222	A1	WO 2004-US25979	20040811

PRIORITY APPLN. INFO: US 2003-495650P 20030815

AB WO2005019222 A UPAB: 20050401

NOVELTY - 4-cycloalkyl amino pyrazolo pyrimidine compound (Ia), its salt, enantiomer or diastereomer is new.

DETAILED DESCRIPTION - 4-cycloalkyl amino pyrazolo pyrimidine compound (Ia), its salt, enantiomer or diastereomer is new.

R1 = (un)substituted benzene with halogen or R2;

R2 = 1-6C alkyl optionally substituted with halogen(s); and

Y = (un)substituted 1-6C alkyl with halogen.

An INDEPENDENT CLAIM is also included for a pharmaceutical composition comprising the compound (Ia) as an active ingredient.

ACTIVITY - Analgesic; Antiparkinsonian; Neuroprotective; Nootropic; Anticonvulsant; Antidepressant; Tranquilizer; Cerebroprotective; Antiinflammatory.

No test details are given.

MECHANISM OF ACTION - NMDA-Antagonist-NR3B.

The compounds were found to have an IC50 value and Ki value of less than 0.1 micro M in the functional and binding assays.

USE - For treating and preventing pain, Parkinson's disease, Alzheimer's disease, epilepsy, depression, anxiety, ischemic brain injury including stroke, chronic, visceral, inflammatory, neuropathic pain syndromes, pain due to traumatic nerve injury, nerve compression or entrapment, post herpetic neuralgia, trigeminal neuralgia, diabetic neuropathy, cancer and chemotherapy, chronic lower back pain, phantom limb pain, HIV or HIV-treatment-induced neuropathy, chronic pelvic pain, neuroma pain, complex regional pain syndrome, chronic arthritic pain and related neuralgia and partial and generalized tonic seizures (claimed).

ADVANTAGE - The pyrimidine compounds are excellent NMDA/NR2B (N-methyl-D-aspartate) antagonists.

Dwg.0/0

L91 ANSWER 294 OF 313 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN

ACCESSION NUMBER: 2005-202583 [21] WPIX

CROSS REFERENCE: 2005-202584 [21]

DOC. NO. CPI: C2005-064866
 TITLE: New 4-cycloalkylaminopyrazolopyrimidine derivatives useful for treating e.g. pain, Parkinson's disease, Alzheimer's disease, epilepsy, depression, anxiety and stroke.
 DERWENT CLASS: B02
 INVENTOR(S): BUTCHER, J; DIECKHAUS, C; LAYTON, M E; LIVERTON, N; MCCAULEY, J A; MCINTYRE, C J; MUNSON, P; PHILLIPS, B T; SANDERSON, P E; THOMPSON, W; WHITTER, W; YOUNG, S D
 PATENT ASSIGNEE(S): (BUTC-I) BUTCHER J; (DIEC-I) DIECKHAUS C; (LAYT-I) LAYTON M E; (LIVE-I) LIVERTON N; (MCCA-I) MCCAULEY J A; (MCIN-I) MCINTYRE C J; (MUNS-I) MUNSON P; (PHIL-I) PHILLIPS B T; (SAND-I) SANDERSON P E; (THOM-I) THOMPSON W; (WHIT-I) WHITTER W; (YOUN-I) YOUNG S D; (MERI) MERCK & CO INC
 COUNTRY COUNT: 108
 PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2005019221	A1	20050303	(200521)*	EN	155
RW: AT BE BG BW CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE					
LS LU MC MW MZ NA NL OA PL PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW					
W: AE AG AL AM AT AU AZ BA BB BG BR BW BY BZ CA CH CN CO CR CU CZ DE					
DK DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG					
KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NA NI NO NZ					
OM PG PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG					
US UZ VC VN YU ZA ZM ZW					
US 2005054658	A1	20050310	(200521)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2005019221	A1	WO 2004-US25961	20040811
US 2005054658	A1 Provisional	US 2003-495650P	20030815
		US 2004-917194	20040812

PRIORITY APPLN. INFO: US 2003-495650P 20030815; US
 2004-917194 20040812

AB WO2005019221 A UPAB: 20050401
 NOVELTY - 4-Cycloalkylaminopyrazolopyrimidine derivatives and their salts or diastereomer are new.
 DETAILED DESCRIPTION - 4-Cycloalkylaminopyrazolopyrimidine derivatives of formula (I) and their salts or diastereomer are new.
 T1 = 1H-pyrazolo(3,4-d)pyrimidin-4-yl (optionally substituted by at least one of halo, R9, OR9, CN, N(R9)2);
 R1 = phenyl or diphenylmethyl (both optionally substituted by at least one of halo, R2, OR2, CN, N(R2)2);
 Y = 1,4-cyclohexylene, -CH2-(cyclopropane-1,2-diyl)-, -CH2CH(CH2-Ca-)-Cb-, R3 or -R3-O-R3-;
 R1(Ca+Cb) = 5 to 7 member fused ring;
 Z = absent, O, 1-6C alkyl, 1-6C alkenyl, C(O), S, SO, SO2 or NR4;
 R4 = 0-6C alkyl or 0-6C alkenyl (both optionally substituted by at least one of halo, R5, OR5, CN, N(R5)2);
 A and B = 0-4C alkyl;
 W = 0-6C alkyl, 0-6C alkenyl (both optionally substituted by at least one of halo, R8, OR8, CN, N(R8)2), absent, O, C(O), S, SO, SO2 or NR7; and

R2 - R9 = H, 0-6C alkyl, 0-6C alkenyl (optionally substituted by at least one halo).

A ring is formed comprising A and B, where an individual carbon atom in A and an individual carbon atom in B optionally bridge the ring, and each member of the ring is optionally substituted by at least one of halo, R6, OR6, CN or N(R6)2.

An INDEPENDENT CLAIM is included for a composition comprising an inert carrier and (I).

ACTIVITY - Analgesic; Antiparkinsonian; Neuroprotective; Nootropic; Anticonvulsant; Antidepressant; Tranquilizer; Cerebroprotective; Vasotropic; Antiinflammatory; Antidiabetic; Antiarthritic; Osteopathic; Gynecological; Antirheumatic; Antigout; Antimigraine; Neuroleptic; Auditory; Ophthalmological; Muscular-Gen.; Antiaddictive.

MECHANISM OF ACTION - N-Methyl-D-aspartate (NMDA)/NR2B antagonist.

Test details are described, but no results given.

USE - For treating pain, Parkinson's disease, Alzheimer's disease, epilepsy, depression, anxiety, and ischemic brain injury including stroke, chronic, visceral, inflammatory and neuropathic pain syndromes, pain resulting from or associated with traumatic nerve injury, nerve compression or entrapment, postherpetic neuralgia, trigeminal neuralgia, diabetic neuropathy, cancer and chemotherapy, chronic lower back pain, phantom limb pain, HIV- and HIV treatment-induced neuropathy, chronic pelvic pain, neuroma pain, complex regional pain syndrome, chronic arthritic pain and related neuralgias, generalized tonic seizures (claimed). Also for treating neuropathic pain (e.g. postherpetic neuralgia, nerve injury, vulvodynia, root avulsions, painful traumatic mononeuropathy, painful polyneuropathy), central pain syndromes and postsurgical pain syndrome (e.g. postmastectomy syndrome, postthoracotomy syndrome, stump pain), osteoarthritis, repetitive motion pain, dental pain, cancer pain, myofascial pain (muscular injury, fibromyalgia), perioperative pain (general surgery, gynecological), chronic pain, dysmenorrhea, as well as pain associated with angina, and inflammatory pain of varied origins (e.g. osteoarthritis, rheumatoid arthritis, rheumatic disease, tenosynovitis and gout), headache, migraine and cluster headache, schizophrenia, traumatic brain injury, cerebral ischemia, amyotrophic lateral sclerosis, Huntington's disease, sensorineural hearing loss, tinnitus, glaucoma, neurological damage caused by epileptic seizures or by neurotoxin poisoning or by impairment of glucose and/or oxygen to the brain, vision loss caused by neurodegeneration of the visual pathway, restless leg syndrome, multi-system atrophy, non-vascular headache, primary hyperalgesia, secondary hyperalgesia, primary allodynia, secondary allodynia, or other pain caused by central sensitization; for preventing dyskinesias, particularly the side effects accompanying normal doses of L-Dopa; for decreasing tolerance and/or dependence to opioid treatment of pain; for treatment of withdrawal syndrome of e.g. alcohol, opioids, and cocaine.

ADVANTAGE - The compounds are potent antagonist of N-methyl-D-aspartate (NMDA) receptors preferably subtype NR2B.
Dwg.0/0

L91 ANSWER 295 OF 313 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
ACCESSION NUMBER: 2005-048537 [05] WPIX
DOC. NO. CPI: C2005-016610
TITLE: New 3-fluoro-piperidine derivatives are NMDA-R2B
antagonists useful for treating and preventing e.g. pain,
migraine, schizophrenia, cluster headache, Alzheimer's
disease, stroke, epilepsy and Parkinson's disease.
DERWENT CLASS: B03
INVENTOR(S): CLAIBORNE, C F; CLAREMON, D A; LIVERTON, N J; MCCAULEY, J

A
 PATENT ASSIGNEE(S): (MERI) MERCK & CO INC
 COUNTRY COUNT: 108
 PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2004108705	A1	20041216	(200505)*	EN	41
RW: AT BE BG BW CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS LU MC MW MZ NA NL OA PL PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW					
W: AE AG AL AM AT AU AZ BA BB BG BR BW BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NA NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW					

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2004108705	A1	WO 2004-US17175	20040528

PRIORITY APPLN. INFO: US 2003-475938P 20030604

AB WO2004108705 A UPAB: 20050124

NOVELTY - 3-Fluoro-piperidines (I) and their salts are new.

DETAILED DESCRIPTION - 3-Fluoro-piperidines of formula (I) and their salts are new.

HetAr = 5-6 membered heteroaromatic ring containing nitrogen atom, thiazolyl or thiadiazolyl, optionally substituted by 1 or 2 of 1-4C alkyl, fluoro, chloro, bromo or iodo;

A = bond or 1-2C alkyl; and

B' = aryl(CH₂)₀₋₃-O-C(O), indanyl(CH₂)₀₋₃-O-C(O), aryl(CH₂)₁₋₃-C(O), aryl-cyclopropyl-C(O), aryl(CH₂)₁₋₃-NH-C(O), (where the aryls are optionally substituted by 1-5 of 1-4C alkyl, fluoro or chloro).

Note: R1 and R2 are not defined in the claims, but defined as the substituents H, 1-4C alkyl, F, Cl, Br or I in the disclosure.

An INDEPENDENT CLAIM is also included for composition which contains an inert carrier and 3-fluoro-piperidines (I) and their salts.

ACTIVITY - Analgesic; Antimigraine; Neuroleptic; Neuroprotective; Antidepressant; Tranquilizer; Nootropic; Cerebroprotective; Anticonvulsant; Antiparkinsonian; Antiinflammatory; Antiarthritic.

MECHANISM OF ACTION - NMDA-Antagonist-R2B.

NR2B NMDA receptor transfected L(tk) cells were plated in 96-well plates and cultured in normal growth medium (Dulbeccos MEM with sodium pyruvate, glucose (4500 mg), glutamine, 10% FCS and geneticin (0.5 mg/ml). NR2B-expression in the cells was induced by adding dexamethasone in the presence of ketamine (500 micro M) for 16-24 hours. To the culture, (3R,4S)-4-methylbenzyl-3-fluoro-4-((pyrimidin-2-yl amino)methyl)piperidine-1-carboxylate (Ia) dissolved in DMSO was added. The antagonistic activity of the compound was evaluated by measuring the fluorescence intensity. The IC50 value of the compound was 0.1 micro M or less.

USE - For treating and preventing pain, migraine, schizophrenia, depression, anxiety, cluster headache, Alzheimer's disease, stroke, epilepsy, Parkinson's disease, chronic, visceral, inflammatory, neuropathic pain syndromes, pain resulting or associated with traumatic nerve injury, nerve compression or entrapment, postherpetic neuralgia, trigeminal neuralgia, diabetic neuropathy, cancer, chemotherapy, lower back pain, phantom limb pain, HIV and HIV treatment

induced neuropathy, chronic pelvic pain, neuroma pain, complex regional pain syndrome, chronic arthritic pain and related neuralgia, epilepsy, and partial and generalized tonic seizures (claimed).
Dwg.0/0

L91 ANSWER 296 OF 313 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
ACCESSION NUMBER: 2004-757816 [74] WPIX
DOC. NO. CPI: C2004-265901
TITLE: New di-aryl substituted triazole are metabotropic glutamate receptor-5 inhibitors useful as medicament for treating e.g. pain disorders, anxiety disorders, Parkinson's disease, depression, epilepsy, memory loss and drug addiction.
DERWENT CLASS: B03
INVENTOR(S): COSFORD, N D P; ROPPE, J R; TEHRANI, L R; WANG, B
PATENT ASSIGNEE(S): (MERI) MERCK & CO INC
COUNTRY COUNT: 108
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2004089306	A2	20041021	(200474)*	EN	42
RW: AT BE BG BW CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS LU MC MW MZ NL OA PL PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW					
W: AE AG AL AM AT AU AZ BA BB BG BR BW BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NA NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW					

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2004089306	A2	WO 2004-US9750	20040331

PRIORITY APPLN. INFO: US 2003-462796P 20030404

AB WO2004089306 A UPAB: 20041117

NOVELTY - Di-aryl substituted triazole derivatives (I) and their salts are new.

DETAILED DESCRIPTION - Di-aryl substituted triazole derivatives of formula (I) and their salts are new.

Either X, Y = (hetero)aryl (where at least one of X and Y is a heteroaryl with N adjacent to the position of attachment to A or B respectively);

X = optionally substituted with 1-7 of halo, CN, NO₂, 1-6C alkyl, 2-6C alkenyl, 2-6C alkynyl, OR₁, NR₁R₂, C(=NR₁)NR₂R₃, N(=NR₁)NR₂R₃, NR₁COR₂, NR₁CO₂R₂, NR₁SO₂R₄, NR₁CONR₂R₃, SR₄, SOR₄, SO₂R₄, SO₂NR₁R₂, COR₁, CO₂R₁, CONR₁R₂, C(NR₁)R₂ or C(NOR₁)R₂ substituents (optionally two substituents are combined to form a (hetero)cycloalkyl ring fused to X), where 1-6C alkyl and (hetero)cycloalkyl ring are each optionally substituted with 1-5 of T₁;

T₁ = halo, CN, 1-6C alkyl, O(0-6C alkyl), O(3-7C cycloalkyl), O(aryl), O(heteroaryl), N(0-6C alkyl)(0-6C alkyl), N(0-6C alkyl)(3-7C cycloalkyl) or N(0-6C alkyl)(aryl);

Y = optionally substituted with 1-7 of halo, CN, NO₂, 1-6C alkyl, 2-6C alkenyl, 2-6C alkynyl, OR₅, NR₅R₆, C(NR₅)NR₆R₇, N(NR₅)NR₆R₇, NR₅COR₆, NR₅CO₂R₆, NR₅SO₂R₈, NR₅CONR₆R₇, SR₈, SOR₈, SO₂R₈, SO₂NR₅R₆, COR₅, CO₂R₅,

CONR5R6, C(NR5)R6 or C(NOR5)R6 substituents (where optionally 2 substituents are combined to form a (hetero)cycloalkyl ring fused to Y), where the 1-6C alkyl and (hetero)cycloalkyl are optionally substituted by 1-5 T1);

W = 3-7C cycloalkyl, hetero3-7C cycloalkyl, 0-6C alkylaryl or 0-6C alkylheteroaryl (optionally substituted with 1-7 of halo, CN, NO₂, 1-6C alkyl, 1-6C alkenyl, 1-6C alkynyl, OR₁, NR₁R₂, C(=NR₁)NR₂R₃, N(=NR₁)NR₂R₃, NR₁COR₂, NR₁CO₂R₂, NR₁SO₂R₄, NR₁CONR₂R₃, SR₄, SOR₄, SO₂R₄, SO₂NR₁R₂, COR₁, CO₂R₁, CONR₁R₂, C(NR₁)R₂ or C(NOR₁)R₂ substituents);

R₁-R₃, R₅-R₇, R₉, R₁₀ = 0-6C alkyl, 3-7C cycloalkyl or (hetero)aryl (all optionally substituted with 1-5 of halo, CN, 1-6C alkyl, O(0-6C alkyl), O(3-7C cycloalkyl), O(aryl), O(heteroaryl), N(0-6C alkyl)(0-6C alkyl), N(0-6C alkyl)(3-7C cycloalkyl) or N(0-6C alkyl)(aryl) substituents);

R₄, R₈ = 1-6C alkyl, 3-7C cycloalkyl or (hetero)aryl (optionally substituted with 1-5 of halo, CN, 1-6C alkyl, O(0-6C alkyl), O(3-7C cycloalkyl), O(aryl), O(heteroaryl), N(0-6C alkyl)(0-6C alkyl), N(0-6C alkyl)(3-7C cycloalkyl) or N(0-6C alkyl)(aryl) substituents);

A = 0-4C alkyl, 0-2C alkyl-SO-0-2C alkyl, 0-2C alkyl-SO₂-0-2C alkyl, 0-2C alkyl-CO-0-2C alkyl, 0-2C alkyl-NR₉CO-0-2C alkyl, 0-2C alkyl-NR₉SO₂-0-2C alkyl or hetero 0-4C alkyl;

B = 0-4C alkyl, 0-2C alkyl-SO-0-2C alkyl, 0-2C alkyl-SO₂-0-2C alkyl, 0-2C alkyl-CO-0-2C alkyl, 0-2C alkyl-NR₁₀CO-0-2C alkyl, 0-2C alkyl-NR₁₀SO₂-0-2C alkyl or hetero 0-4C alkyl;

Z = 3-7C cycloalkyl, hetero3-7C cycloalkyl, 0-6C alkylaryl or 0-6C alkylheteroaryl (optionally substituted with 1-7 of halo, CN, NO₂, 1-6C alkyl, 1-6C alkenyl, 1-6C alkynyl, OR₁, NR₁R₂, C(NR₁)NR₂R₃, N(NR₁)NR₂R₃, NR₁COR₂, NR₁CO₂R₂, NR₁SO₂R₄, NR₁CONR₂R₃, SR₄, SOR₄, SO₂R₄, SO₂NR₁R₂, COR₁, CO₂R₁, CONR₁R₂, C(=NR₁)R₂ or C(NOR₁)R₂ substituents);

R₁₁ = halo, 0-6C alkyl, 0-6C alkoxyl, =O, =N(0-4C alkyl) or N(0-4C alkyl)(0-4C alkyl).

Any alkyl is optionally substituted with 1-5 of halo substituents;

any N may be an N-oxide; and

one of W and Z is optionally absent.

Three of A₁, A₂, A₃, A₄, A₅ are N, the remaining are C, and one of A₁ and A₄ must be N, but not both A₁ and A₄ are N.

An INDEPENDENT CLAIM is also included for a composition comprising (I).

ACTIVITY - Analgesic; Antimicrobial; Antiinflammatory; Neuroleptic; Antiparkinsonian; Anticonvulsant; Nootropic; Muscular-Gen.; Tranquilizer; Antidepressant; Antiaddictive; CNS-Gen.; Hypnotic; Anorectic; Antismoking; Neuroprotective.

MECHANISM OF ACTION - Metabotropic glutamate receptor-5 (mGluR-5) inhibitor.

(I) were tested for their mGluR-5 activity using calcium flux assay. The results showed that the median inhibitory concentration of (I) was 10 micro M.

USE - (I) are useful as a medicament in the treatment of pain disorders (acute pain, persistent pain, chronic pain, inflammatory pain or neuropathic pain), extrapyramidal motor function disorders (Parkinson's disease, progressive supramuscular palsy, Huntington's disease, Gilles de la Tourette syndrome or tardive dyskinesia), anxiety disorders, Parkinson's disease, depression, epilepsy, cognitive disfunction, drug addiction, circadian rhythm, sleep disorders, obesity, bipolar disorder, psychosis, drug withdrawal, tobacco withdrawal, memory loss, cognitive impairment, dementia, Alzheimer's disease, schizophrenia or panic (all claimed).

ADVANTAGE - (I) has less side effects.

Dwg.0/0

L91 ANSWER 297 OF 313 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
 ACCESSION NUMBER: 2004-594035 [57] WPIX
 CROSS REFERENCE: 2004-365416 [34]; 2004-376060 [35]; 2004-400064 [37]
 DOC. NO. CPI: C2004-216089
 TITLE: Composition, useful to treat side effects e.g. nausea, vomiting, anxiety or fatigue, comprises milnacipran and an ion-exchange resin.
 DERWENT CLASS: B05
 INVENTOR(S): FLEMING, A B; HIRSH, J; RARIY, R V
 PATENT ASSIGNEE(S): (COLL-N) COLLEGIUM PHARM INC
 COUNTRY COUNT: 108
 PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2004067039	A1	20040812	(200457)*	EN	41
RW:	AT BE BG BW CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE				
	LS LU MC MW MZ NL OA PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW				
W:	AE AG AL AM AT AU AZ BA BB BG BR BW BY BZ CA CH CN CO CR CU CZ DE				
	DK DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG				
	KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NA NI NO NZ				
	OM PG PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG				
	US UZ VC VN YU ZA ZM ZW				
US 2004228830	A1	20041118	(200477)		
AU 2004207578	A1	20040812	(200568)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2004067039	A1	WO 2004-US2346	20040128
US 2004228830	A1 Provisional	US 2003-443237P	20030128
	Provisional	US 2003-443618P	20030129
	Provisional	US 2003-458993P	20030328
	Provisional	US 2003-468470P	20030506
	Provisional	US 2003-490060P	20030724
		US 2004-766124	20040128
AU 2004207578	A1	AU 2004-207578	20040128

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2004207578	A1 Based on	WO 2004067039

PRIORITY APPLN. INFO: US 2003-490060P 20030724; US
 2003-443237P 20030128; US
 2003-443618P 20030129; US
 2003-458993P 20030328; US
 2003-468470P 20030506; US
 2004-766124 20040128

AB WO2004067039 A UPAB: 20051024

NOVELTY - Multiparticulate milnacipran composition (I) for oral administration comprises particles (d) consisting of milnacipran (a) complexed with an ion-exchange resin (r).

DETAILED DESCRIPTION - An INDEPENDENT CLAIM is also included for preparation of (I).

ACTIVITY - Antiemetic; Analgesic; Tranquilizer; Cardiovascular-Gen.;

Uropathic; Hypertensive; Laxative; Auditory; Antipyretic; Gynecological; Muscular-Gen.; Immunomodulator; Gastrointestinal-Gen.; Sedative; Antidepressant; Nootropic; Antiinflammatory; Antimigraine.

MECHANISM OF ACTION - **Norepinephrine (NE) uptake inhibitor; Serotonin (5-HT) uptake inhibitor.**

USE - (I) is useful to treat side effects (preferably nausea, vomiting, headache, tremulousness, anxiety, panic attacks, palpitations, urinary retention, orthostatic hypotension, diaphoresis, chest pain, rash, weight gain, back pain, constipation, vertigo, increased sweating, agitation, hot flushes, tremors, fatigue, somnolence, dyspepsia, dysoria, nervousness, dry mouth, abdominal pain, irritability or insomnia) (claimed). (I) is also useful to treat **depression**, fibromyalgia syndrome, chronic fatigue syndrome, **pain**, attention deficit/hyperactivity disorder, visceral pain syndromes e.g. irritable bowel syndrome, noncardiac chest pain, functional dyspepsia, interstitial cystitis, vulvodynia, urethral syndrome, orchialgia, depressive disorders (major depressive disorder, dysthymia, atypical depression), anxiety disorders (generalized anxiety disorder, phobias, obsessive compulsive disorder, panic disorder, post-traumatic stress disorder), premenstrual dysphoric disorder, temperomandibular disorder, atypical face pain, migraine headache and tension headache.

ADVANTAGE - (I) in a liquid dosage form, provides delayed or extended release of (a) to produce a therapeutic effect over approximately 24 hours when administered to a patient, with diminished incidence and reduced intensity relative to one or more immediate release milnacipran side effects (claimed).

Dwg.0/0

L91 ANSWER 298 OF 313 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
 ACCESSION NUMBER: 2004-294977 [27] WPIX
 DOC. NO. CPI: C2004-112814
 TITLE: New fused heterobicyclo substituted phenyl derivatives are metabotropic glutamate receptor-subtype 5 modulators useful for the treatment or prevention of e.g. schizophrenia, anxiety and depression.
 DERWENT CLASS: B02
 INVENTOR(S): CAMPBELL, B T; GUNZNER, J L; MUNOZ, B; STEARNS, B A; VERNIER, J A; WANG, B
 PATENT ASSIGNEE(S): (MERI) MERCK & CO INC; (CAMP-I) CAMPBELL B T; (GUNZ-I) GUNZNER J L; (MUNO-I) MUNOZ B; (STEA-I) STEARNS B A; (VERN-I) VERNIER J A; (WANG-I) WANG B
 COUNTRY COUNT: 106
 PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2004024074	A2	20040325	(200427)*	EN	37
RW:	AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS				
	LU MC MW MZ NL OA PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW				
W:	AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK				
	DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KR				
	KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NI NO NZ OM PG PH				
	PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG US UZ VC				
	VN YU ZA ZM ZW				
AU 2003267087	A1	20040430	(200462)		
EP 1539749	A2	20050615	(200539)	EN	
R:	AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LI LT LU LV				
	MC MK NL PT RO SE SI SK TR				

US 2005240021 A1 20051027 (200571)

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2004024074	A2	WO 2003-US28344	20030909
AU 2003267087	A1	AU 2003-267087	20030909
EP 1539749	A2	EP 2003-749563	20030909
		WO 2003-US28344	20030909
US 2005240021	A1 Provisional	US 2002-410549P	20020913
		WO 2003-US28344	20030909
		US 2005-527044	20050308

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2003267087	A1 Based on	WO 2004024074
EP 1539749	A2 Based on	WO 2004024074

PRIORITY APPLN. INFO: US 2002-410549P 20020913; US
2005-527044 20050308

AB WO2004024074 A UPAB: 20040426

NOVELTY - Fused heterobicyclo substituted phenyl derivatives (I) and their salts are new.

DETAILED DESCRIPTION - Fused heterobicyclo substituted phenyl derivatives (I) and their salts are new.

X1, X2, X4, X6 = C, N, S or O;

X3, X5 = C or N;

Y = 0-4C alkyl, aryl or heteroaryl;

Q = (CH₂)_{n1}

Q1 = (CH₂)_{n2}

R1, R2 = halo, 0-4C alkyl or pyridyl; and

n1, n2 = 0-1.

provided that at least one of X1, X2, X3, X4, X5 and X6 is N; at most one of X1, X2, X4 and X6 is S or O.

AN INDEPENDENT CLAIM is also included for a composition comprising (I).

ACTIVITY - Analgesic; Antiinflammatory; Tranquilizer; Antidepressant; Neuroleptic; Antiaddictive; Nootropic; Neuroprotective; Antiparkinsonian; Anticonvulsant; Muscular-Gen.; Eating-Disorders-Gen.

MECHANISM OF ACTION - Metabotropic glutamate receptor-subtype 5 (mGluR5) modulator. (I) were assessed for mGluR5 modulatory activity using calcium flux assay in mouse fibroblast Ltk - cells (the hmGluR5a/L38 cell line). The median inhibitory concentration of 3-(3-methoxy-4-(pyridin-2-yl)phenyl)imidazo(1,5-a)pyridine hydrochloride was less than 5 μ M.

USE - (I) are useful for the treatment or prevention of pain, pain disorders (preferably acute pain, persistent pain, chronic pain, inflammatory **pain** or neuropathic **pain**), anxiety, **depression**, bipolar disorders, psychosis, drug withdrawal, tobacco withdrawal, memory loss, cognitive impairment, dementia, Alzheimer's disease, schizophrenia, pain, disorders of extrapyramidal motor function (preferably Parkinson's disease, progression supramuscular palsy, Huntington's disease, Gille de la Tourette syndrome or tardive dyskinesia), anxiety disorders (preferably panic attack, agoraphobia or specific phobias, obsessive-compulsive disorders, post-traumatic stress disorder, acute stress disorder, generalized anxiety disorders, eating disorders, substance-induced anxiety disorder or nonspecified anxiety),

epilepsy, cognitive dysfunction and drug addiction (claimed).

ADVANTAGE - (I) has minimum side effects.

Dwg.0/0

L91 ANSWER 299 OF 313 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
 ACCESSION NUMBER: 2003-788196 [74] WPIX
 DOC. NO. CPI: C2003-217616
 TITLE: New di-aryl substituted tetrazole compounds useful for
 treating and preventing e.g. **pain** disorder,
 anxiety disorder and **depression**.
 DERWENT CLASS: B02 B03 C02
 INVENTOR(S): CHEN, C; COSFORD, N D P; EASTMAN, B W; HUANG, D; POON, S
 F; REGER, T R; ROPPE, J R; SMITH, N D; REGER, T S
 PATENT ASSIGNEE(S): (MERI) MERCK & CO INC; (CHEN-I) CHEN C; (COSF-I) COSFORD
 N D P; (EAST-I) EASTMAN B W; (HUAN-I) HUANG D; (POON-I)
 POON S F; (REGE-I) REGER T S; (ROPP-I) ROPPE J R;
 (SMIT-I) SMITH N D
 COUNTRY COUNT: 103
 PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2003077918	A1	20030925	(200374)*	EN	85
RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS					
LU MC MW MZ NL OA PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW					
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK					
DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KR KZ					
LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NI NO NZ OM PH PL PT					
RO RU SC SD SE SG SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA					
ZM ZW					
AU 2003213783	A1	20030929	(200432)		
EP 1485093	A1	20041215	(200482)	EN	
R: AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LI LT LU LV					
MC MK NL PT RO SE SI SK TR					
US 2005153986	A1	20050714	(200547)		
JP 2005526081	W	20050902	(200559)		159

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2003077918	A1	WO 2003-US7074	20030307
AU 2003213783	A1	AU 2003-213783	20030307
EP 1485093	A1	EP 2003-711474	20030307
		WO 2003-US7074	20030307
US 2005153986	A1 Provisional	US 2002-363456P	20020312
		WO 2003-US7074	20030307
		US 2004-506479	20040901
JP 2005526081	W	JP 2003-575971	20030307
		WO 2003-US7074	20030307

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2003213783	A1 Based on	WO 2003077918
EP 1485093	A1 Based on	WO 2003077918
JP 2005526081	W Based on	WO 2003077918

PRIORITY APPLN. INFO: US 2002-363456P 20020312; US
2004-506479 20040901

AB WO2003077918 A UPAB: 20031117

NOVELTY - Di-aryl substituted tetrazole compounds (I) are new.

DETAILED DESCRIPTION - Di-aryl substituted tetrazole compounds of formula (I) or its salts are new.

X = (hetero)aryl (optionally mono- to hepta-substituted by T (where optionally two substituents are combined to form (hetero)cycloalkyl ring fused to X, and -1-6C alkyl and (hetero)cycloalkyl are both optionally mono- to penta-substituted by T1));

T = halo, -CN, NO₂, -1-6C alkyl, -1-6C alkenyl, -1-6C alkynyl, -OR₁, -NR₁R₂, -C(=NR₁)NR₂R₃, -N(=NR₁)NR₂R₃, -NR₁COR₂, -NR₁CO₂R₂, -NR₁SO₂R₄, -NR₁CONR₂R₃, -SR₄, -SOR₄, -SO₂R₄, -SO₂NR₁R₂, -COR₁, -CO₂R₁, -CONR₁R₂, -C(=NR₁)R₂ or -C(=NOR₁)R₂;

T₁ = halo, -CN, -1-6C alkyl, -O(0-6C alkyl), -O(3-7C cycloalkyl), -O(aryl), -N(0-6C alkyl)(0-6C alkyl), -N(0-6C alkyl)(3-7C cycloalkyl), or -N(0-6C alkyl)(aryl);

Y' = (hetero)aryl (optionally mono- to hepta-substituted by halo, -CN, NO₂, -1-6C alkyl, -1-6C alkenyl, -1-6C alkynyl, -OR₅, -NR₅R₆, -C(=NR₅)NR₆R₇, -N(=NR₅)NR₆R₇, -NR₅COR₆, -NR₅CO₂R₆, -NR₅SO₂R₈, -NR₅CONR₆R₇, -SR₈, -SOR₈, -SO₂R₈, -SO₂NR₅R₆, -COR₅, -CO₂R₅, -CONR₅R₆, -C(=NR₅)R₆ or -C(=NOR₅)R₆ (where optionally two substituents are combined to form (hetero)cycloalkyl ring fused to Y', and -1-6C alkyl and (hetero)cycloalkyl are both optionally mono- to penta-substituted by T₁));

R₁ - R₃, R₅ - R₇, R₉, R₁₀ = 0-6C alkyl, 3-7C cycloalkyl, or (hetero)aryl (all optionally mono- to penta-substituted by T₁);

R₄, R₈ = 1-6C alkyl, -3-7C cycloalkyl, or (hetero)aryl (all optionally mono- to penta-substituted by T₁);

A = 0-4C alkyl, 0-2C alkyl-SO-0-2C alkyl-, 0-2C alkyl-SO₂-0-2C alkyl-, 0-2C alkyl-CO-0-2C alkyl-, 0-2C alkyl-NR₉CO-0-2C alkyl-, 0-2C alkylNR₉SO₂-0-2C alkyl- or hetero-0-4C alkyl;

W', Z' = 3-7C cycloalkyl, hetero-3-7C cycloalkyl, 0-6C alkylaryl, or 0-6C alkylheteroaryl (all optionally mono- to hepta-substituted by T);

B' = 0-4C alkyl, 0-2C alkyl-SO-0-2C alkyl-, 0-2C alkyl-SO₂-0-2C alkyl-, 0-2C alkyl-CO-0-2C alkyl-, 0-2C alkyl-NR₁₀CO-0-2C alkyl-, 0-2C alkylNR₁₀SO₂-0-2C alkyl- or hetero-1-4C alkyl.

Provided that: at least one of X and Y is a heteroaryl with N adjacent to the position of attachment to A or B respectively; one of W and Z is optionally absent; and any N may be an N-oxide.

An INDEPENDENT CLAIM is included for a pharmaceutical composition comprising (I) and a carrier.

ACTIVITY - Analgesic; Antiinflammatory; Tranquilizer; Eating-Disorder-Gen.; Antidepressant; Neuroleptic; Nootropic; Antiaddictive; Antismoking; Neuroprotective; Antiparkinsonian; Anticonvulsant; Muscular-Gen.; CNS-Gen.; Hypnotic; Anorectic.

MECHANISM OF ACTION - Metabotropic glutamate receptor-5 modulator.

(I) was tested for metabotropic glutamate receptor-5 inhibitory activity and IC₅₀ was found to be at most 10 micro M and at most 100 micro M in the calcium flux assay and PI assay, respectively. No specific result for specific compound given.

USE - For treating and preventing pain disorder (e.g. acute pain, chronic pain, inflammatory pain or neuropathic pain), anxiety disorder (e.g. panic attack, agoraphobia or specific phobias, obsessive-compulsive disorders, post-traumatic stress disorder, acute stress disorder, generalized anxiety disorder, eating disorder, substance-induced anxiety disorder or nonspecific anxiety disorder), depression, bipolar disorder, psychosis, drug withdrawal, tobacco withdrawal, memory loss, cognitive impairment, dementia, Alzheimer's disease, schizophrenia, panic, extrapyramidal motor function disorder (e.g. Parkinson's disease,

progressive supramuscular palsy, Huntington's disease, Gilles de la Tourette syndrome or tardive dyskinesia), epilepsy, circadian rhythm, sleep disorder (e.g. shift-work induced sleep disorder or jet-lag) and obesity.

ADVANTAGE - The compound inhibits metabotropic glutamate receptor-5 with minimal side effects.

Dwg.0/0

L91 ANSWER 300 OF 313 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
 ACCESSION NUMBER: 2003-646033 [61] WPIX
 CROSS REFERENCE: 2003-449132 [42]; 2003-607838 [57]; 2003-618015 [58];
 2003-636590 [60]; 2004-330064 [30]
 DOC. NO. CPI: C2003-176749
 TITLE: New heteroaryl substituted pyrroles useful in the
 treatment or prevention of e.g. **pain**,
depression and bipolar disorder.
 DERWENT CLASS: B02 B03
 INVENTOR(S): COSFORD, N D P; HUANG, D; SMITH, N D
 PATENT ASSIGNEE(S): (MERI) MERCK & CO INC; (COSF-I) COSFORD N D P; (HUA-I)
 HUANG D; (SMIT-I) SMITH N D
 COUNTRY COUNT: 102
 PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2003059904	A1	20030724	(200361)*	EN	67
RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR IE IT KE LS LU					
MC MW MZ NL OA PT SD SE SI SK SL SZ TR TZ UG ZM ZW					
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK					
DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KR KZ					
LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO					
RU SC SD SE SG SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM					
ZW					
AU 2002364906	A1	20030730	(200421)		
EP 1458710	A1	20040922	(200462)	EN	
R: AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR IE IT LI LT LU LV MC					
MK NL PT RO SE SI SK TR					
US 2005085514	A1	20050421	(200531)		
JP 2005516969	W	20050609	(200538)		55

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2003059904	A1	WO 2002-US40486	20021217
AU 2002364906	A1	AU 2002-364906	20021217
EP 1458710	A1	EP 2002-801209	20021217
		WO 2002-US40486	20021217
US 2005085514	A1 Provisional	US 2001-343262P	20011221
		WO 2002-US40486	20021217
		US 2004-499393	20040617
JP 2005516969	W	WO 2002-US40486	20021217
		JP 2003-560007	20021217

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2002364906	A1 Based on	WO 2003059904

EP 1458710 A1 Based on WO 2003059904
JP 2005516969 W Based on WO 2003059904

PRIORITY APPLN. INFO: US 2001-343262P 20011221; US
2004-499393 20040617

AB WO2003059904 A UPAB: 20050616

NOVELTY - Heteroaryl substituted pyrroles (I) are new.

DETAILED DESCRIPTION - Heteroaryl substituted pyrroles of formula (I) or their salt are new.

X, Y = (hetero)aryl (optionally mono- - hepta-substituted by Q);

Q = halo, -CN, NO₂, 1-6C alkyl (optionally mono- - penta-substituted by T), 1-6C alkenyl, 1-6C alkynyl, -OR₁, -NR₁R₂, -C(=NR₁)NR₂R₃, N(=NR₁)NR₂R₃, -NR₁COR₂, -NR₁CO₂R₂, -NR₁SO₂R₄, -NR₁CONR₂R₃, -SR₄, -SOR₄, -SO₂R₄, -SO₂NR₁R₂, -COR₁, -CO₂R₁, -CONR₁R₂, -C(=NR₁)R₂ or C(=NOR₁)R₂;

T = halo, -CN, -1-6C alkyl, -O-(0-6C alkyl), -O-(3-7C cycloalkyl), -O-(hetero)aryl, -N-(0-6C alkyl)(0-6C alkyl), -N-(0-6C alkyl)(3-7C cycloalkyl) or -N-(0-6C alkyl)(aryl);

R₁ - R₃ = 0-6C alkyl, 3-7C cycloalkyl or (hetero)aryl (all optionally mono- - penta-substituted by T);

R₄ = 1-6C alkyl, 3-7C cycloalkyl or (hetero)aryl (all optionally mono- - penta-substituted by T);

A = 0-4C alkyl, 0-2C-alkyl-SO-(0-2C alkyl), 0-2C-alkyl-SO₂-(0-2C alkyl), 0-2C-alkyl-CO-(0-2C alkyl), 0-2C-alkyl-NR₉CO-(0-2C alkyl), 0-2C-alkyl-NR₉SO₂-(0-2C alkyl) or hetero-(0-4C alkyl);

B' = 0-4C alkyl, 0-2C-alkyl-SO-(0-2C alkyl), 0-2C-alkyl-SO₂-(0-2C alkyl), 0-2C-alkyl-CO-(0-2C alkyl), 0-2C-alkyl-NR₁₀CO-(0-2C alkyl), 0-2C-alkyl-NR₁₀SO₂-(0-2C alkyl) or hetero-(0-4C alkyl);

R₉, R₁₀ = 0-6C alkyl, 3-7C cycloalkyl or (hetero)aryl (all optionally mono- - penta-substituted by T); and

R₁₁ - R₁₃ = halo, 0-6C alkyl, 0-6C alkoxy, O, =N(0-4C alkyl) or -N(0-4C alkyl) (where 1-6C alkyl is optionally mono- - penta-substituted by T).

Two substituents of X and Y are combined to form (hetero)cycloalkyl ring (both optionally mono- - penta-substituted by T) fused to X.

Optionally two of R₁₁ - R₁₃ are combined to form (hetero)cycloalkyl (optionally mono- - penta-substituted by T), or (hetero)aryl fused to pyrrole group. Any N is optionally an N-oxide. Any alkyl is optionally mono- - nano-substituted by halo.

ACTIVITY - Analgesic; Antidepressant; Antiaddictive; Nootropic; Neuroprotective; Neuroleptic; Tranquilizer; Antipsychotic; Antiparkinsonian; Anticonvulsant; Antiaddictive; Anorectic; Anabolic; Antiinflammatory; Hypnotic.

MECHANISM OF ACTION - Metabotropic glutamate receptor-5 (mGluR5) modulator.

The mGluR5 inhibitory activity of (I) was examined against hmGluR5a receptor expressed in mouse fibroblast Ltk cells (the hmGluR5a/L38 cell line) using calcium flux assay. (I) showed IC₅₀ of less than 10 (preferably less than 1 micro M).

USE - For treating or preventing pain (e.g. acute pain, persistent pain, chronic pain, inflammatory pain and neuropathic pain), depression, bipolar disorder, psychosis, drug withdrawal, memory loss, cognitive impairment, dementia, Alzheimer's disease, schizophrenia, panic, disorders of extrapyramidal motor function (e.g. Parkinson's disease, progressive supramuscular palsy, Huntington's disease, Gilles de la Tourette syndrome, and tardive dyskinesia), anxiety disorders (e.g. panic attack, agoraphobia or specific phobias, obsessive-compulsive disorders, post-traumatic stress disorder, acute stress disorder, generalized anxiety disorder, eating disorder, substance-induced anxiety disorder and non-specified anxiety disorder),

epilepsy, drug abuse, drug addiction, circadian rhythm, sleep disorder (e.g. shift-work induced sleep disorder and jet-lag) and obesity (all claimed).

ADVANTAGE - The compounds inhibit mGluR5 with minimal side effects.
Dwg.0/0

L91 ANSWER 301 OF 313 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
ACCESSION NUMBER: 2003-636590 [60] WPIX
CROSS REFERENCE: 2003-449132 [42]; 2003-607838 [57]; 2003-618015 [58];
2003-646033 [61]; 2004-330064 [30]
DOC. NO. CPI: C2003-173981
TITLE: New heteroaryl substituted imidazole compounds useful as
metabotropic glutamate receptor modulator in the
treatment of psychiatric and mood disorders e.g.
schizophrenia, anxiety, depression and bipolar disorders.
DERWENT CLASS: B03
INVENTOR(S): COSFORD, N D P; HUANG, D; SMITH, N D
PATENT ASSIGNEE(S): (MERI) MERCK & CO INC; (COSF-I) COSFORD N D P; (HUA-I)
HUANG D; (SMIT-I) SMITH N D
COUNTRY COUNT: 102
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2003053922	A2	20030703	(200360)*	EN	23
RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SI SK SL SZ TR TZ UG ZM ZW W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SC SD SE SG SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW					
AU 2002360621	A1	20030709	(200428)		
EP 1458385	A2	20040922	(200462)	EN	
R: AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI SK TR					
US 2004259917	A1	20041223	(200504)		
JP 2005516950	W	20050609	(200538)		37

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2003053922	A2	WO 2002-US40237	20021216
AU 2002360621	A1	AU 2002-360621	20021216
EP 1458385	A2	EP 2002-795893	20021216
		WO 2002-US40237	20021216
US 2004259917	A1 Provisional	US 2001-341963P	20011219
		WO 2002-US40237	20021216
		US 2004-499392	20040617
JP 2005516950	W	WO 2002-US40237	20021216
		JP 2003-554639	20021216

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2002360621	A1 Based on	WO 2003053922
EP 1458385	A2 Based on	WO 2003053922

JP 2005516950 W Based on WO 2003053922

PRIORITY APPLN. INFO: US 2001-341963P 20011219; US
2004-499392 20040617

AB WO2003053922 A UPAB: 20050616

NOVELTY - Heteroaryl substituted imidazole compounds (I) or their salts are new.

DETAILED DESCRIPTION - Heteroaryl substituted imidazole compounds of formula (I) or their salts are new.

X, Y = (hetero)aryl (optionally mono- to hepta-substituted by T;
T = 1-6C alkyl (optionally mono- to penta-substituted by T1), halo, CN, NO₂, -NR₁R₂, -C(=NR₁)NR₂R₃, -N(=NR₁)NR₂R₃, -NR₁COR₂, -NR₁CO₂R₂, -NR₁SO₂R₄, -NR₁CONR₂R₃, -SO₂NR₁R₂, -CONR₁R₂, -C(=NR₁)R₂ or -C(=NOR₁)R₂), 2-6C alkenyl, 2-6C alkynyl, -OR₁, -SR₄, -SOR₄, -SO₂R₄, -COR₁ or -CO₂R₁;

X+T+T, Y+T+T = (hetero)cycloalkyl (optionally mono- to penta-substituted by T1)

T1 = -1-6C alkyl, -O(0-6C alkyl), -O(3-7C cycloalkyl), -N(0-6C alkyl)(0-6C alkyl), -N(0-6C alkyl)(3-7C cycloalkyl), -N(0-6C alkyl)(aryl), halo, CN or -O(hetero)aryl);

R1 - R3, R9, R10 = 0-6C alkyl, -3-7C cycloalkyl or (hetero)aryl (all optionally mono- to penta-substituted by T1);

R4 = -1-6C alkyl, -3-7C cycloalkyl or (hetero)aryl (all optionally substituted by T1);

A = -0-2C alkyl-NR₉CO-0-2C alkyl or -0-2C alkyl-NR₉SO₂-0-2C alkyl or T2;

T2 = -0-4C alkyl, -0-2C alkyl-SO-0-2C alkyl, -0-2C alkyl-SO₂-0-2C alkyl, -0-2C alkyl-CO-0-2C alkyl or -hetero-0-4C alkyl;

B = -0-2C alkyl-NR₁₀CO-0-2C alkyl, -0-2C alkyl-NR₁₀SO₂-0-2C alkyl or T2;

R11, R12 = -0-6C alkyl, =N(0-4C alkyl), -N(0-4C alkyl)(0-4C alkyl), halo, -0-6C alkoxyl or =O; and
provided that:

- (1) any alkyl is optionally mono- - penta-substituted by halo
- (2) any N is optionally N-oxide; and
- (3) at least one of X and Y is a heteroaryl with N adjacent to the position of attachment to A or B respectively.

An INDEPENDENT CLAIM is included for a pharmaceutical composition comprising (I) and a carrier.

ACTIVITY - Analgesic; Tranquilizer; Antidepressant; Nootropic; Antiaddictive; Antismoking; Neuroprotective; Neuroleptic; Antiparkinsonian; Anticonvulsant; Muscular-Gen.; CNS-Gen.; Eating Disorder-Gen; Anorectic.

MECHANISM OF ACTION - Metabotropic Glutamate Receptor Subtype 5 (mGluR5) Modulator.

(I) were examined against the huGluR5a receptor stably expressed in mouse fibroblast Ltk-cells as described in Daggett et al., Neuropharmacology 34:871 - 886 (1995). (I) showed IC₅₀ of less than 10 micro M, (preferably less than 100 nM). No results for specific compounds given.

USE - (I) are used for treating or preventing pain (including acute, persistent, chronic, inflammatory and neuropathic pain), anxiety, **depression**, bipolar disorder, psychosis, drug withdrawal, tobacco withdrawal, memory loss, cognitive impairment, dementia, Alzheimer's disease, schizophrenia, panic disorders, extrapyramidal motor function (e.g. Parkinson's disease, progressive supramuscular palsy, Huntington's disease, Gilles de la Tourette syndrome and tardive dyskinesia), anxiety disorders (e.g. panic attack, agoraphobia and specific phobias, obsessive-compulsive disorders, post-traumatic stress disorder, acute stress disorder, generalized anxiety disorder,

eating disorder, substance-induced anxiety disorder and nonspecific anxiety disorder), epilepsy, inflammatory pain, cognitive dysfunction, drug addiction, drug abuse, circadian rhythm, sleep disorder (e.g. shift-work induced sleep disorder and jet lag) and obesity (all claimed).

ADVANTAGE - The compounds are potent metabotropic glutamate receptor subtype 5 (mGluR5) modulators, and exhibit minimal side effects.
Dwg.0/0

L91 ANSWER 302 OF 313 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
 ACCESSION NUMBER: 2003-618015 [58] WPIX
 CROSS REFERENCE: 2003-449132 [42]; 2003-607838 [57]; 2003-636590 [60];
 2003-646033 [61]; 2004-330064 [30]
 DOC. NO. CPI: C2003-168551
 TITLE: New heteroaryl substituted pyrazole useful for treating
 e.g. psychiatric and mood disorder.
 DERWENT CLASS: B02 B03
 INVENTOR(S): CHEN, C; COSFORD, N D P; EASTMAN, B W; HUANG, D; MUNOZ,
 B; PRASIT, P; SMITH, N D
 PATENT ASSIGNEE(S): (MERI) MERCK & CO INC; (CHEN-I) CHEN C; (COSF-I) COSFORD
 N D P; (EAST-I) EASTMAN B W; (HUAN-I) HUANG D; (MUNO-I)
 MUNOZ B; (PRAS-I) PRASIT P; (SMIT-I) SMITH N D
 COUNTRY COUNT: 102
 PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2003051833	A2	20030626	(200358)*	EN	66
RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SI SK SL SZ TR TZ UG ZM ZW					
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SC SD SE SG SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW					
AU 2002359714	A1	20030630	(200420)		
EP 1458383	A2	20040922	(200462)	EN	
R: AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI SK TR					
US 2005026963	A1	20050203	(200511)		
JP 2005516934	W	20050609	(200538)		136

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2003051833	A2	WO 2002-US40147	20021213
AU 2002359714	A1	AU 2002-359714	20021213
EP 1458383	A2	EP 2002-794267	20021213
		WO 2002-US40147	20021213
US 2005026963	A1 Provisional	US 2001-341382P	20011218
		WO 2002-US40147	20021213
		US 2004-497122	20040526
JP 2005516934	W	WO 2002-US40147	20021213
		JP 2003-552720	20021213

FILING DETAILS:

PATENT NO	KIND	PATENT NO

AU 2002359714	A1 Based on	WO 2003051833
EP 1458383	A2 Based on	WO 2003051833
JP 2005516934	W Based on	WO 2003051833

PRIORITY APPLN. INFO: US 2001-341382P 20011218; US
2004-497122 20040526

AB WO2003051833 A UPAB: 20050616

NOVELTY - Heteroaryl substituted pyrazole (I) or its salt is new.

DETAILED DESCRIPTION - Heteroaryl substituted pyrazole of formula (I), or its salt is new.

X, Y = (hetero)aryl (optionally mono - hepta substituted by Q);

Q = halo, -CN, NO₂, 1-6C alkyl (optionally mono to penta-substituted by T), 1-6C alkenyl, 1-6C alkynyl, -OR₁, -NR₁R₂, -C(=NR₁)NR₂R₃, N(=NR₁)NR₂R₃, -NR₁COR₂, -NR₁CO₂R₂, -NR₁SO₂R₄, -NR₁CONR₂R₃, -SR₄, -SOR₄, -SO₂R₄, -SO₂NR₁R₂, -COR₁, -CO₂R₁, -CONR₁R₂, -C(=NR₁)R₂ or C(=NOR₁)R₂;

T = halo, -CN, -1-6C alkyl, -O-(0-6C alkyl), -O-(3-7C cycloalkyl), -O-((hetero)aryl), -N-(0-6C alkyl)(0-6C alkyl), -N-(0-6C alkyl)(3-7C cycloalkyl) or -N-(0-6C alkyl)(aryl);

R₁ - R₃ = 0-6C alkyl, 3-7C cycloalkyl or (hetero)aryl (optionally mono to penta-substituted by T);

R₄ = 1-6C alkyl, 3-7C cycloalkyl or (hetero)aryl (optionally mono to penta-substituted by T);

A = 0-4C alkyl, 0-2C-alkyl-SO-(0-2C)-alkyl, 0-2C-alkyl-SO₂-(0-2C)-alkyl, 0-2C-alkyl-CO-(0-2C)-alkyl, 0-2C-alkyl-NR₉CO-(0-2C)-alkyl, 0-2C-alkyl-NR₉SO₂-(0-2C)-alkyl or hetero-(0-4C)-alkyl;

B' = 0-4C alkyl, 0-2C-alkyl-SO-(0-2C)-alkyl, 0-2C-alkyl-SO₂-(0-2C)-alkyl, 0-2C-alkyl-CO-(0-2C)-alkyl, 0-2C-alkyl-NR₁₀CO-(0-2C)-alkyl, 0-2C-alkyl-NR₁₀SO₂-(0-2C)-alkyl or hetero-(0-4C)-alkyl;

R₉, R₁₀ = 0-6C alkyl, 3-7C cycloalkyl or (hetero)aryl (optionally mono- to penta-substituted by T);

A₁, A₂ = N or CR₁₂;

R₁₁, R₁₂ = halo, 0-6C alkyl, 0-6C alkoxy or -N(0-4C alkyl)(0-4C alkyl) (1-6C alkyl is optionally mono to penta-substituted by T); and

R₁₁+R₁₂ = (hetero)cycloalkyl (optionally mono to penta-substituted by T) or (hetero)aryl ring fused to the pyrazole group.

Two substituents of X and Y are combined to form a cycloalkyl or heterocycloalkyl ring (both optionally mono to penta-substituted by T) fused to X. At least one of X and Y is a heteroaryl with N adjacent to the position of attachment to A or B' respectively. R₁₁ and R₁₂ form =O, =N(0-4C alkyl) using a bond from the adjoining double bond. Any N may be an N-oxide. One of A₁ and A₂ is N, then the other is CR₁₂. Any alkyl is optionally mono to nano-substituted by halo.

Provided that when X is 2-pyridyl, A₁ is N, A₂ is CH, R₁₁ and R₁₂ are H, and A and B' are absent, then Y is other than 4-methoxyphenyl or 2,5-dimethoxyphenyl.

An INDEPENDENT CLAIM is also included for a composition comprising (I) optionally in combination with another therapeutic agent.

ACTIVITY - Analgesic; Tranquilizer; Antidepressant; Nootropic; Neuroleptic; Antiaddictive; Antismoking; Anabolic; Antiinflammatory; Neuroprotective; Antiparkinsonian; Muscular; Anticonvulsant; Anorectic; Hypnotic.

MECHANISM OF ACTION - Metabotropic glutamate receptor-subtype 5 (mGluR5) inhibitor/modulator.

(I) was tested for mGluR5 inhibitory activity and showed an IC₅₀ value of less than 10 micro M. But no specific results are given.

USE - For the treatment or prevention of pain disorder (e.g. acute pain, persistent pain, chronic pain, inflammatory pain and neuropathic pain), anxiety, depression, bipolar disorder, psychosis, drug withdrawal, tobacco withdrawal, memory loss,

cognitive impairment, dementia, Alzheimer's disease, schizophrenia and panic), extrapyramidal motor function disorders (e.g. Parkinson's disease, progressive supramuscular palsy, Huntington's disease, Gilles de la Tourette syndrome and tardive dyskinesia), anxiety disorders (e.g. panic attack, agoraphobia or specific phobias, obsessive-compulsive disorders, post traumatic stress disorder, acute stress disorder, generalized anxiety disorder, eating disorder, substance-induced anxiety disorder and non-specified anxiety disorder), neuropathic **pain**, Parkinson's Disease, **depression**, epilepsy, inflammatory **pain**, cognitive dysfunction, drug addiction, drug abuse and drug withdrawal, bipolar disorders, circadian rhythm, sleep disorders (e.g. shift-work induced sleep disorder and jet-lag) and obesity (all claimed).

ADVANTAGE - The compounds inhibit mGluR5 with fewer side effects.
Dwg.0/0

L91 ANSWER 303 OF 313 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
ACCESSION NUMBER: 2003-607838 [57] WPIX
CROSS REFERENCE: 2003-449132 [42]; 2003-618015 [58]; 2003-636590 [60];
2003-646033 [61]; 2004-330064 [30]
DOC. NO. CPI: C2003-165566
TITLE: New heteroaryl substituted triazole derivatives useful
for the treatment of psychiatric and mood disorders e.g.
schizophrenia, anxiety, depression, panic and bipolar
disorder.
DERWENT CLASS: B02 B03
INVENTOR(S): COSFORD, N D P; PRASIT, P; ROPPE, J R; SMITH, N D;
TEHRANI, L R
PATENT ASSIGNEE(S): (MERI) MERCK & CO INC; (COSF-I) COSFORD N D P; (PRAS-I)
PRASIT P; (ROPP-I) ROPPE J R; (SMIT-I) SMITH N D;
(TEHR-I) TEHRANI L R
COUNTRY COUNT: 102
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2003051315	A2	20030626	(200357)*	EN	28
RW:	AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR IE IT KE LS LU				
MC MW MZ NL OA PT SD SE SI SK SL SZ TR TZ UG ZM ZW					
W:	AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK				
DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KR KZ					
LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO					
RU SC SD SE SG SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM					
ZW					
AU 2002366388	A1	20030630	(200420)		
EP 1458708	A2	20040922	(200462)	EN	
R:	AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR IE IT LI LT LU LV MC				
MK NL PT RO SE SI SK TR					
US 2005020585	A1	20050127	(200509)		
JP 2005516920	W	20050609	(200538)		48

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2003051315	A2	WO 2002-US41720	20021213
AU 2002366388	A1	AU 2002-366388	20021213
EP 1458708	A2	EP 2002-805227	20021213
		WO 2002-US41720	20021213
US 2005020585	A1 Provisional	US 2001-341582P	20011218

		WO 2002-US41720	20021213
		US 2004-499391	20040617
JP 2005516920	W	WO 2002-US41720	20021213
		JP 2003-552248	20021213

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2002366388	A1 Based on	WO 2003051315
EP 1458708	A2 Based on	WO 2003051315
JP 2005516920	W Based on	WO 2003051315

PRIORITY APPLN. INFO: US 2001-341582P 20011218; US
2004-499391 20040617

AB WO2003051315 A UPAB: 20050616

NOVELTY - Heteroaryl substituted triazole derivatives (I) are new.

DETAILED DESCRIPTION - Heteroaryl substituted triazole derivatives of formula (I) or their salts are new.

X = (hetero)aryl (optionally substituted by 1-7 of Q);

Q = halo, -CN, NO₂, 1-6C alkyl (optionally substituted by 1-5 of T'), 2-6C alkenyl, 2-6C alkynyl, -OR₁, -NR₁R₂, -C(=NR₁)NR₂R₃, N(=NR₁)NR₂R₃, -NR₁COR₂, -NR₁CO₂R₂, -NR₁SO₂R₄, -NR₁CONR₂R₃, -SR₄, -SOR₄, -SO₂R₄, -SO₂NR₁R₂, -COR₁, -CO₂R₁, -CONR₁R₂, -C(=NR₁)R₂, or C(=NOR₁)R₂;

T' = halo, -CN, 1-6C alkyl, -O-(0-6C alkyl), -O-(3-7C cycloalkyl), -O-((hetero)aryl), -N-(0-6C alkyl)(0-6C alkyl), -N-(0-6C alkyl)(3-7C cycloalkyl), or -N-(0-6C alkyl)(aryl);

A₁ - A₅ = N or C;

R₁ - R₃, R₅ - R₇, R₉ and R₁₀ = 0-6C alkyl, 3-7C cycloalkyl or (hetero)aryl (all optionally substituted by 1-5 T');

R₄ and R₈ = 1-6C alkyl, 3-7C cycloalkyl, or (hetero)aryl (all optionally substituted by 1-5 of T');

A = 0-4C alkyl, 0-2C alkyl-SO-(0-2C alkyl)-, 0-2C alkyl-SO₂-(0-2C alkyl), 0-2C alkyl-CO-(0-2C alkyl)-, 0-2C alkyl-NR₉CO-(0-2C alkyl), 0-2C alkyl-NR₉SO₂-(0-2C alkyl) or -hetero-(0-4C alkyl);

Y' = (hetero)aryl (optionally substituted by 1-7 of Q₁);

Q₁ = halo, -CN, NO₂, 1-6C alkyl (optionally substituted by 1-5 of T'), 2-6C alkenyl, 2-6C alkynyl, -OR₅, -NR₅R₆, -C(=NR₅)NR₆R₇, N(=NR₅)NR₆R₇, -NR₅COR₆, -NR₅CO₂R₆, -NR₅SO₂R₈, -NR₅CONR₆R₇, -SR₈, -SOR₈, -SO₂R₈, -SO₂NR₅R₆, -COR₅, -CO₂R₅, -CONR₅R₆, -C(=NR₅)R₆, or C(=NOR₅)R₆;

B' = 0-4C alkyl, 0-2C alkyl-SO-(0-2C alkyl)-, 0-2C alkyl-SO₂-(0-2C alkyl)-, 0-2C alkyl-CO-(0-2C alkyl), 0-2C alkyl-NR₁₀CO-(0-2C alkyl)-, 0-2C alkyl-NR₁₀SO₂-(0-2C alkyl), or -hetero-(0-4C alkyl); and

R₁₁ = halo, -0-6C alkyl, -0-6C alkoxyl, =O, =N(0-4C alkyl), or N(0-4C alkyl)(0-4C alkyl).

Optionally two substituents of X and Y' are combined to form a (hetero)cycloalkyl ring (both optionally substituted by 1-5 T) fused to X and Y' respectively. At least one of X and Y is (hetero)aryl with N adjacent to the position of attachment to A or B respectively. Provided that:

- (1) three of A₁ - A₅ are N and the remaining are C;
- (2) one of A₁ and A₄ must be N but both A₁ and A₄ are N; and
- (3) when X is 2-pyridyl, A₁ and A₃ are C, A₂, A₄ and A₅ are N, A and B are direct bond and R₁₁ is OH, then Y' is not unsubstituted phenyl or 4-methoxyphenyl.

ACTIVITY - Analgesic; Antiinflammatory; Tranquilizer; Antidepressant; Nootropic; Neuroleptic; Antismoking; Neuroprotective; Antiparkinsonian; Anticonvulsant; Muscular; Antiaddictive; Anorectic.

MECHANISM OF ACTION - Metabotropic glutamate receptor-subtype 5

(mGluR5) modulator/inhibitor.

The inhibitory activity of 2-(1-(3-chlorophenyl)-1H-1,2,4-triazol-3-yl)pyridine (A) against hmGluR5a receptor stably expressed in mouse fibroblast Ltk-cells was tested in terms of intracellular calcium ((Ca²⁺)_i). The hmGluR5a/L38-20 cells were plated onto 96-well plates and loaded with fura-2 (3 μM) for 1 hour. The cell plate was transferred to a 96-channel fluorimeter which was integrated into a fully automated plate handling and liquid delivery system. The glutamate (10 μM) was added to the well and the glutamate-evoked increase in (Ca²⁺)_i in the presence of the screening compound was measured. (A) showed an IC₅₀ value of 10 μM.

USE - For treatment or prevention of a pain disorder (e.g. acute pain, persistent pain, chronic pain, inflammatory **pain** and neuropathic **pain**), anxiety, **depression**, bipolar disorder, psychosis, drug withdrawal, tobacco withdrawal, memory loss, cognitive impairment, dementia, Alzheimer's disease, schizophrenia, extrapyramidal motor function disorder (e.g. Parkinson's disease, progressive supramuscular palsy, Huntington's disease, Gilles de la Tourette syndrome and tardive dyskinesia), anxiety disorder (e.g. panic attack, agoraphobia or specific phobias, obsessive-compulsive disorders, post-traumatic stress disorder, acute stress disorder, generalized anxiety disorder, eating disorder, substance-induced anxiety disorder and non-specified anxiety disorder), epilepsy, drug addiction, drug abuse, circadian rhythm, sleep disorder (e.g. shift-work induced sleep disorder and jet-lag) and obesity (all claimed).

ADVANTAGE - The compounds inhibit metabotropic glutamate receptor-subtype 5 (mGluR5) with fewer side effects.
Dwg.0/0

L91 ANSWER 304 OF 313 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
ACCESSION NUMBER: 2003-541545 [51] WPIX
DOC. NO. CPI: C2003-146953
TITLE: New fused heterobicyclo substituted phenyl compounds
useful for treating or preventing e.g. **pain**,
anxiety, **depression**, bipolar disorder,
psychosis, or drug withdrawal.
DERWENT CLASS: B02
INVENTOR(S): ARRUDA, J; BONNEFOUS, C; CAMPBELL, B T; CUBE, R V; MUNOZ,
B; STEARNS, B; VERNIER, J; WANG, B; ZHAO, X
PATENT ASSIGNEE(S): (MERI) MERCK & CO INC; (ARRU-I) ARRUDA J; (BONN-I)
BONNEFOUS C; (CAMP-I) CAMPBELL B T; (CUBE-I) CUBE R V;
(MUNO-I) MUNOZ B; (STEA-I) STEARNS B; (VERN-I) VERNIER J;
(WANG-I) WANG B; (ZHAO-I) ZHAO X
COUNTRY COUNT: 102
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG

WO 2003048137	A1	20030612	(200351)*	EN	57
RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR IE IT KE LS LU					
MC MW MZ NL OA PT SD SE SK SL SZ TR TZ UG ZM ZW					
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK					
DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KR KZ					
LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO					
RU SC SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA					
ZM ZW					
AU 2002365892	A1	20030617	(200419)		
EP 1453815	A1	20040908	(200459)	EN	
R: AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR IE IT LI LT LU LV MC					
MK NL PT RO SE SI SK TR					

US 2005065340 A1 20050324 (200526)
 JP 2005514382 W 20050519 (200538) 98

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2003048137	A1	WO 2002-US38201	20021126
AU 2002365892	A1	AU 2002-365892	20021126
EP 1453815	A1	EP 2002-804470	20021126
		WO 2002-US38201	20021126
US 2005065340	A1 Provisional	US 2001-334547P	20011130
		WO 2002-US38201	20021126
		US 2004-497452	20041109
JP 2005514382	W	WO 2002-US38201	20021126
		JP 2003-549329	20021126

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2002365892	A1 Based on	WO 2003048137
EP 1453815	A1 Based on	WO 2003048137
JP 2005514382	W Based on	WO 2003048137

PRIORITY APPLN. INFO: US 2001-334547P 20011130; US
 2004-497452 20041109

AB WO2003048137 A UPAB: 20040210

NOVELTY - Fused heterobicyclo substituted phenyl compounds (I) are new.

DETAILED DESCRIPTION - Fused heterobicyclo substituted phenyl compounds of formula (I) and their salts are new.

dotted line = optional double bond;

X = N, CH or NH;

Y = O or N-R4;

Z1-Z4 = N, NH, CH or CH2;

R1 = 1-6C alkyl, 1-4C alkoxy, 3-6C cycloalkyl, 0-4C alkyl-phenyl, 0-4C alkyl-pyridyl, 0-4C alkyl-imidazolyl, 0-4C alkyl-pyrazolyl, 0-4C alkyl-triazolyl, 0-4C alkyl-tetrazolyl, 0-4C alkyl-dioxolanyl, 0-4C alkyl-thiazolyl, 0-4C alkyl-piperidinyl, 0-4C alkyl-pyrrolidinyl, 0-4C alkyl-morpholinyl, 0-4C alkyl-pyrimidinyl, 2-6C alkynyl-thiazolyl or N(0-4C alkyl)2 (all optionally substituted by 1-5 T), OH, halo or CN;

T = halo, OH, CN, 1-6C alkyl, 1-4C alkoxy, N(0-4C alkyl)2, 0-4C alkyl-COO-0-4C alkyl, 0-4C alkyl-morpholinyl or 0-4C alkyl-benzoxazolyl;

R2 = H, halo, OH, CN, N(0-4C alkyl)2, NO2, 1-6C alkyl, 1-4C alkoxy, 0-4C alkyl-phenyl or 1-4C alkoxy-phenyl (all optionally substituted by 1-3 halo, OH, CN or 1-4C alkoxy);

R3 = H or -1-4C alkoxy;

R4 = 0-4C alkyl; and

R5 = H, halo or 1-4C alkyl;

provided that:

(i) one of Z1-Z4 is optionally N or NH; and

(ii) when X = N and Y = O, then Z1-Z4 = CH, R1 = 1-6C alkyl, 3-6C cycloalkyl, 0-4C alkyl-triazolyl, 0-4C alkyl-imidazolyl, 0-4C alkyl-pyrazolyl, 0-4C alkyl-tetrazolyl, 0-4C alkyl-pyrrolidinyl, 0-4C alkyl-piperidinyl, 0-4C alkyl-pyridyl, 0-4C alkyl-pyrimidinyl or 0-4C alkyl-morpholinyl (all optionally substituted by 1-5 T), and R2 = 0-4C alkyl-phenyl, 1-6C alkyl, NO2, N(0-4C alkyl)2, 1-6C alkoxy-phenyl or 1-6C alkoxy (all optionally substituted by halo, OH, CN or 1-4C alkoxy).

ACTIVITY - Analgesic; Tranquilizer; Antidepressant; Nootropic;

Neuroleptic; Antiaddictive; Antismoking; Neuroprotective;
Antiparkinsonian; Eating-Disorders-Gen.; Anticonvulsant.

MECHANISM OF ACTION - Metabotropic Glutamate Receptor-5 Modulator.
Compounds (I) were tested for mgluR5 inhibitory activity using calcium flux assay in terms of intracellular calcium (see Daggett et al., Neuropharmacology, 34:871-886 (1995)). Compounds (I) exhibited mGluR5 inhibitory activity of less than 5 μ M (preferred compounds (I) less than 50 nM). No specific data given.

USE - For treating or preventing pain (e.g. acute pain, persistent pain, chronic pain, inflammatory **pain** and neuropathic **pain**), anxiety, **depression**, bipolar disorder, psychosis, drug withdrawal, tobacco withdrawal, memory loss, cognitive impairment, dementia, Alzheimer's disease, schizophrenia, panic, disorder of extrapyramidal motor function (e.g. Parkinson's disease, progressive supramuscular palsy, Huntington's disease, Gilles de la Tourette syndrome or tardive dyskinesia), anxiety disorder (e.g. panic attack, agoraphobia or specific phobias, obsessive-compulsive disorders, post-traumatic stress disorder, acute stress disorder, generalized anxiety disorder, eating disorders, substance-induced anxiety disorder or nonspecified anxiety disorder), neuropathic pain, epilepsy, inflammatory pain, cognitive dysfunction, drug addition (claimed) and drug abuse.

ADVANTAGE - (I) Displays minimal side effects.
Dwg.0/0

L91 ANSWER 305 OF 313 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
ACCESSION NUMBER: 2003-449132 [42] WPIX
CROSS REFERENCE: 2003-607838 [57]; 2003-618015 [58]; 2003-636590 [60];
2003-646033 [61]; 2004-330064 [30]
DOC. NO. CPI: C2003-119158
TITLE: New heteroaryl substituted tetrazole compounds useful for
e.g. treatment of acute pain, Alzheimer's disease,
schizophrenia, Parkinson's disease, anxiety disorders,
epilepsy, drug addiction, and obesity.
DERWENT CLASS: B02 B03
INVENTOR(S): CHEN, C; COSFORD, N D; REGER, T; ROPPE, J; SMITH, N;
COSFORD, N D P; REGER, T S; ROPPE, J R; SMITH, N D
PATENT ASSIGNEE(S): (MERI) MERCK & CO INC; (CHEN-I) CHEN C; (COSF-I) COSFORD
N D P; (REGE-I) REGER T S; (ROPP-I) ROPPE J R; (SMIT-I)
SMITH N D
COUNTRY COUNT: 101
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2003029210	A2	20030410	(200342)*	EN	60
RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SK SL SZ TR TZ UG ZM ZW					
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW					
EP 1434773	A2	20040707	(200444)	EN	
R: AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI SK TR					
AU 2002341921	A1	20030414	(200461)		
US 2004186295	A1	20040923	(200463)		
JP 2005508344	W	20050331	(200523)		226

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2003029210	A2	WO 2002-US31294	20021001
EP 1434773	A2	EP 2002-776076	20021001
		WO 2002-US31294	20021001
AU 2002341921	A1	AU 2002-341921	20021001
US 2004186295	A1 Provisional	US 2001-327132P	20011004
		WO 2002-US31294	20021001
		US 2004-491613	20040402
JP 2005508344	W	WO 2002-US31294	20021001
		JP 2003-532460	20021001

FILING DETAILS:

PATENT NO	KIND	PATENT NO
EP 1434773	A2 Based on	WO 2003029210
AU 2002341921	A1 Based on	WO 2003029210
JP 2005508344	W Based on	WO 2003029210

PRIORITY APPLN. INFO: US 2001-327132P 20011004; US
2004-491613 20040402

AB WO2003029210 A UPAB: 20050411

NOVELTY - Heteroaryl substituted tetrazole compounds (I) are new.

DETAILED DESCRIPTION - Heteroaryl substituted tetrazole compounds of formula (I), or their salts are new.

X = Q (optionally mono-heptasubstituted by Q2);

Q2 = 1-6C alkyl (optionally mono-pentasubstituted by Q1), halo, CN, NO2, 1-6C alkenyl, 1-6C alkynyl, OR1, NR1R2, C(=NR1)NR2R3, N(=NR1)NR2R3, NR1COR2, NR1CO2R2, NR1SO2R4, NR1CONR2R3, SR4, SOR4, SO2R4, SO2NR1R2, COR1, CO2R1, CONR1R2, C(=NR1)R2, or C(=NOR1)R2;

Q2+Q2 = (hetero)cycloalkyl ring fused to X (optionally mono-pentasubstituted by Q1);

Q1 = halo, CN, 1-6C alkyl, O(0-6C alkyl), O(3-7C cycloalkyl), O-(hetero)aryl, N(0-6C alkyl)(0-6C alkyl), N(0-6C alkyl)(3-7C cycloalkyl), or N(0-6C alkyl)(aryl);

Q = (hetero)aryl;

Y = Q (optionally mono-heptasubstituted by Q3);

Q3 = 1-6C alkyl (optionally mono-pentasubstituted by Q1), halo, CN, NO2, 1-6C alkenyl, 1-6C alkynyl, OR5, NR5R6, C(=NR5)NR6R7, N(=NR5)NR6R7, NR5COR6, NR5CO2R6, NR5SO2R8, NR5CONR6R7, -SR8, SOR8, SO2R8, SO2NR5R6, COR5, CO2R5, CONR5R6, C(=NR5)R6, or C(=NOR5)R6;

Q3+Q3 = (hetero)cycloalkyl ring fused to Y (optionally mono-pentasubstituted by Q1);

R1-R3, R5-R7, R9, R10 = 0-6C alkyl, 3-7C cycloalkyl, or (hetero)aryl (all optionally mono-pentasubstituted by Q1);

R4, R8 = 1-6C alkyl, 3-7C cycloalkyl, or (hetero)aryl (all optionally mono-pentasubstituted by Q1);

A = 0-4C alkyl, 0-2C alkyl-SO-(0-2C)alkyl, 0-2C alkyl-SO2-(0-2C)alkyl, 0-2C alkyl-CO-(0-2C)alkyl, 0-2C alkyl-NR9CO-(0-2C)alkyl, 0-2C alkyl-NR9SO2-(0-2C)alkyl or hetero(0-4C)alkyl;

B' = 0-4C alkyl, 0-2C alkyl-SO-(0-2C)alkyl, 0-2C alkyl-SO2-(0-2C)alkyl, 0-2C alkyl-CO-(0-2C)alkyl, 0-2C alkyl-NR10CO-(0-2C)alkyl, 0-2C alkyl-NR10SO2-(0-2C)alkyl or hetero(0-4C)alkyl; and

N = N-oxide.

Provided that at least one of X and Y is a heteroaryl with N adjacent to the position of attachment to A or B' respectively.

An INDEPENDENT CLAIM is also included for a pharmaceutical composition comprising (I) and a carrier.

ACTIVITY - Analgesic; Antiinflammatory; Tranquilizer; Antidepressant; Nootropic; Neuroleptic; Antiaddictive; Neuroprotective; Antiparkinsonian; Anticonvulsant; Vulnerary; Antimicrobial; Anorectic.

MECHANISM OF ACTION - Metabotropic glutamate receptor-subtype 5 (mGluR5) inhibitor. The activity of 2-(2-(3-chlorophenyl)-2H-tetrazol-5-yl)pyridine (A) against mGluR5 inhibitor was performed by calcium flux assay. (A) showed an IC50 value of 10 micro M.

USE - Compounds of (I) can be used for treating and preventing pain (e.g. acute pain, persistent pain, chronic pain, inflammatory pain, and neuropathic pain), anxiety, depression, bipolar disorder, psychosis, drug withdrawal, tobacco withdrawal, memory loss, cognitive impairment, dementia, Alzheimer's disease, schizophrenia, panic, extrapyramidal motor function (e.g. Parkinson's disease, progressive supramuscular palsy, Huntington's disease, Gilles de la Tourette syndrome, and tardive dyskinesia), anxiety disorders (e.g. panic attack, agoraphobia or specific phobias, obsessive-compulsive disorder, post-traumatic stress disorder, acute stress disorder, generalized anxiety disorder, eating disorder, substance-induced anxiety disorder, and non-specified anxiety disorder), epilepsy, cognitive dysfunction, drug addiction, circadian rhythm and sleep disorder (e.g. shift-work induced sleep disorder and jet-lag), and obesity (all claimed).

ADVANTAGE - (I) are potent inhibitors of mGluR5 with minimal side effects.

Dwg.0/0

L91 ANSWER 306 OF 313 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
 ACCESSION NUMBER: 2002-723244 [78] WPIX
 DOC. NO. CPI: C2002-204733
 TITLE: New R-(-)-N-methyl-3-((2-methyl-4-hydroxyphenyl)oxy)-3-phenyl-1-aminopropane useful for treating e.g. depression.
 DERWENT CLASS: B05
 INVENTOR(S): MATTIUZ, E L; SAUER, J; WHEELER, W J; WONG, D T; MATTIUTZ, E L
 PATENT ASSIGNEE(S): (ELIL) LILLY & CO ELI; (MATT-I) MATTIUZ E L; (SAUE-I) SAUER J; (WHEE-I) WHEELER W J; (WONG-I) WONG D T
 COUNTRY COUNT: 101
 PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2002070457	A1	20020912	(200278)*	EN	28
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ					
NL OA PT SD SE SL SZ TR TZ UG ZM ZW					
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK					
DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR					
KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT					
RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VN YU ZA ZM					
ZW					
FI 2003001191	A	20030825	(200369)		
LU 91038	A	20030911	(200372)		
NO 2003003921	A	20031105	(200380)		
GB 2389851	A	20031224	(200403)		
EP 1379492	A1	20040114	(200410)	EN	
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT					
RO SE SI TR					
HU 2003003341	A2	20040128	(200415)		

DK 2003001267	A	20031106	(200417)	
BR 2002007716	A	20040323	(200422)	
SE 2003002361	A	20030903	(200422)	
ES 2201942	A1	20040316	(200424)	
KR 2003092012	A	20031203	(200424)	
US 2004082666	A1	20040429	(200429)	
CZ 2003002380	A3	20040317	(200430)	
AU 2002245385	A1	20020919	(200433)	
SK 2003001063	A3	20040608	(200441)	
CN 1494526	A	20040505	(200447)	
JP 2004525912	W	20040826	(200456)	46
ES 2201942	B2	20041216	(200506)	
ZA 2003006882	A	20050223	(200519)	36
GB 2389851	B	20050525	(200536)	
NZ 527431	A	20050527	(200537)	
US 2005209341	A1	20050922	(200563) #	
SE 526598	C2	20051018	(200570)	

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2002070457	A1	WO 2002-US3385	20020220
FI 2003001191	A	WO 2002-US3385	20020220
		FI 2003-1191	20030825
LU 91038	A	LU 2002-91038	20020220
		WO 2002-US3385	20020220
NO 2003003921	A	WO 2002-US3385	20020220
		NO 2003-3921	20030904
GB 2389851	A	WO 2002-US3385	20020220
		GB 2003-23169	20031003
EP 1379492	A1	EP 2002-713538	20020220
		WO 2002-US3385	20020220
HU 2003003341	A2	WO 2002-US3385	20020220
		HU 2003-3341	20020220
DK 2003001267	A	WO 2002-US3385	20020220
		DK 2003-1267	20030904
BR 2002007716	A	BR 2002-7716	20020220
		WO 2002-US3385	20020220
SE 2003002361	A	WO 2002-US3385	20020220
		SE 2003-2361	20030903
ES 2201942	A1	ES 2003-50052	20020220
KR 2003092012	A	KR 2003-711635	20030905
US 2004082666	A1	WO 2002-US3385	20020220
		US 2003-468553	20030821
CZ 2003002380	A3	WO 2002-US3385	20020220
		CZ 2003-2380	20020220
AU 2002245385	A1	AU 2002-245385	20020220
SK 2003001063	A3	WO 2002-US3385	20020220
		SK 2003-1063	20020220
CN 1494526	A	CN 2002-806025	20020220
JP 2004525912	W	JP 2002-569778	20020220
		WO 2002-US3385	20020220
ES 2201942	B2	ES 2003-50052	20020220
ZA 2003006882	A	ZA 2003-6882	20030903
GB 2389851	B	WO 2002-US3385	20020220
		GB 2003-23169	20031003
NZ 527431	A	NZ 2002-527431	20020220
		WO 2002-US3385	20020220

US 2005209341	A1 Cont of	US 2003-468553	20030821
		US 2005-125348	20050509
SE 526598	C2	WO 2002-US3385	20020220
		SE 2003-2361	20030903

FILING DETAILS:

PATENT NO	KIND	PATENT NO
LU 91038	A Based on	WO 2002070457
GB 2389851	A Based on	WO 2002070457
EP 1379492	A1 Based on	WO 2002070457
HU 2003003341	A2 Based on	WO 2002070457
BR 2002007716	A Based on	WO 2002070457
CZ 2003002380	A3 Based on	WO 2002070457
AU 2002245385	A1 Based on	WO 2002070457
SK 2003001063	A3 Based on	WO 2002070457
JP 2004525912	W Based on	WO 2002070457
GB 2389851	B Based on	WO 2002070457
NZ 527431	A Based on	WO 2002070457

PRIORITY APPLN. INFO: US 2001-273730P 20010306; US
2005-125348 20050509

AB WO 200270457 A UPAB: 20021204

NOVELTY - R-(-)-N-methyl-3-((2-methyl-4-hydroxyphenyl)oxy)-3-phenyl-1-aminopropane or its salt is new.

DETAILED DESCRIPTION - R-(-)-N-methyl-3-((2-methyl-4-hydroxyphenyl)oxy)-3-phenyl-1-aminopropane of formula (I) or its salt is new.

ACTIVITY - Antidepressant; antimigraine; analgesic; antialcoholic; antismoking; vasotropic; tranquilizer; nootropic; uropathic; virucide; vulnerary; antipsoriatic; antiallergic; anti-inflammatory; gynecological.

MECHANISM OF ACTION - **Norepinephrine and serotonin uptake inhibitor.**

A dialysate of a Sprague-Dawley rat implanted with microdialysis probes was collected in a loop (20 micro l) and assayed for 5-HT and NE. The injection (20 micro l) goes onto the column with a mobile phase which resolves NE and 5-HT:75 mM potassium acetate, 0.5 mM ethylenediaminetetraacetic acid, 1.4 mM sodium octanesulfonic acid and 8% methanol. The mobile phase for the amine column was delivered with a flow programmable pump at an initial flow rate of 0.2 ml/minutes increasing to 0.3 ml/minutes at 5 minutes then decreasing back to 0.2 ml/minutes at 26 minutes with a total run time of 30 minutes. Flow programming was used to elute the 5-HT within 25 minutes time period. The basal levels were measured for at least 90 minutes prior to drug administration.

R-(-)-N-methyl-3-((2-methyl-4-hydroxyphenyl)oxy)-3-phenyl-1-aminopropane was found to inhibit the uptake of serotonin with a K_i of 43 nM and norepinephrine with a K_i of 3 nM.

USE - For **inhibiting uptake of norepinephrine and serotonin** in mammals (claimed); in the treatment of disorder including **depression**, migraine **pain**, bulimia, premenstrual syndrome or late luteal phase syndrome, alcoholism, tobacco abuse, panic disorder, anxiety, general pain, post-traumatic syndrome, memory loss, dementia of aging, social phobia, attention deficit/hyperactivity disorder, psoriasis, oppositional defiant disorder, conduct disorder, borderline personality disorder, obsessive compulsive disorder, chronic fatigue syndrome, premature ejaculation, erectile difficulty, anorexia nervosa, disorders of sleep, autism, mutism, allergic rhinitis, cold symptoms, narcolepsy,

incontinence, trichotillomania, trigeminal neuralgia, dental pain and
temperomandibular joint dysfunction pain.

ADVANTAGE - (I) exhibits uptake of norepinephrine
and serotonin inhibitory activity.

Dwg.0/0

L91 ANSWER 307 OF 313 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
ACCESSION NUMBER: 2002-404505 [43] WPIX
CROSS REFERENCE: 2001-328151 [34]
DOC. NO. CPI: C2002-113611
TITLE: New 2,3-disubstituted quinuclidines used to modulate
monoamine transmitter system useful for treating e.g.
cocaine abuse, alcoholism, anxiety, depression,
Parkinson's disease, chronic pain and
neurological disorders.
DERWENT CLASS: B02
INVENTOR(S): ISTVAN, E; KOZIKOWSKI, A; SAKAMURI, S; SHAOMENG, W;
ENYEDEY, I; WANG, S
PATENT ASSIGNEE(S): (GEOU) UNIV GEORGETOWN; (ENYE-I) ENYEDEY I; (KOZI-I)
KOZIKOWSKI A; (SAKA-I) SAKAMURI S; (WANG-I) WANG S
COUNTRY COUNT: 98
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2002015906	A1	20020228	(200243)*	EN	60
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW					
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PH PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW					
AU 2001086561	A	20020304	(200247)		
EP 1315493	A1	20030604	(200337)	EN	
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR					
JP 2004506686	W	20040304	(200417)		89
US 2005131051	A1	20050616	(200540)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2002015906	A1	WO 2001-US25991	20010821
AU 2001086561	A	AU 2001-86561	20010821
EP 1315493	A1	EP 2001-966017	20010821
		WO 2001-US25991	20010821
JP 2004506686	W	WO 2001-US25991	20010821
		JP 2002-520827	20010821
US 2005131051	A1 Provisional	US 2000-226581P	20000821
		WO 2001-US25991	20010821
		US 2004-362164	20040912

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2001086561	A Based on	WO 2002015906
EP 1315493	A1 Based on	WO 2002015906

JP 2004506686 W Based on WO 2002015906

PRIORITY APPLN. INFO: US 2000-226581P 20000821; US
2004-362164 20040912

AB WO 200215906 A UPAB: 20050624

NOVELTY - New 2,3-disubstituted quinuclidines of formula (I) and (II) and their salts are new.

DETAILED DESCRIPTION - Disubstituted quinuclidine compounds of formula (I) and (II) and their salts are new.

R1 = H, 1-15C alkyl, 2-15C alkenyl, 3-6C cycloalkyl, mono-, di-, tri-, tetra- or penta- substituted aryl or heteroaryl, (CH₂)_n-aryl, CO₂R₃, COO-(CH₂)_nR₃, (CH₂)_nCOOR₃, C(O)R₃, C(O)NHR₃ or an optionally substituted oxadiazole;R2 = H, 1-15C alkyl, 2-15C alkenyl, 3-10C cycloalkyl, mono-, di-, tri-, tetra- or penta-substituted aryl or heteroaryl, optionally substituted naphthyl, 1,3-benzodioxole, fluorene, indole, isoquinoline, quinoline, pyridine, pyrimidine, anthracene or (CH₂)_n-Ph;

R3 = 1-5C alkyl, 2-5C alkenyl, benzyl, substituted aryl or heteroaryl;

n = 1-7;

The heteroaryl comprises N, O or S and the optional mono or multi substituents on the aryl or heteroaryl are selected from 1-5C alkyl, 2-5C alkenyl, H, F, Cl, Br, I, NO-2, NHR or OR; R = 1-7C alkyl

INDEPENDENT CLAIMS are made for the following:

(1) a method of diagnosis of a condition where at least one of dopamine, serotonin and norepinephrine flow plays a role comprising contacting a sample of a body fluid with a labeled compound (I) or (II);

(2) a method of preparing (I) or (II); and

(3) a labeled compound of formula (I) or (II).

ACTIVITY - Antidepressant, anxiolytic, anorectic, antiparkinsonian, antialcohol, analgesic, tranquilizer; antiaddictive; neuroleptic; nootropic.

MECHANISM OF ACTION - Dopamine inhibitor, serotonin (5-HT) inhibitor and norepinephrine inhibitor.

2-Butyl-3-(4-chloro-phenyl)-1-aza-bicyclo(2.2.2)oct-2-ene hydrochloride exhibited Ki values (nM) of 32 (plus or minus)5, 47(plus or minus)2 and 74(plus or minus)2 for dopamine, **serotonin** (5-HT) and **norepinephrine reuptake inhibition** respectively.USE - Compounds (I) and (II) are used to treat conditions or diseases which require modulation of the monoamine neurotransmitter system (e.g. dopamine, serotonin or norepinephrine) e.g. cocaine abuse, depression, anxiety, eating disorders, Parkinson's disease, alcoholism, neurological disorders, chronic pain and obsessive-compulsive disorder.
Dwg.0/7

L91 ANSWER 308 OF 313 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN

ACCESSION NUMBER: 2002-205549 [26] WPIX

CROSS REFERENCE: 2000-237538 [20]; 2002-163306 [21]; 2002-215830 [27];
2003-708635 [67]; 2004-373599 [35]

DOC. NO. CPI: C2002-062966

TITLE: New 1-(4-Chloro-phenyl)-cyclobutyl compounds are useful as intermediates for producing sibutramine metabolites, which are useful for treating, e.g. neuropathic **pain, depression**, Parkinson's disease and migraine.

DERWENT CLASS: B05

INVENTOR(S): FANG, Q K; HAN, Z; KRISHNAMURTHY, D; SENANAYAKE, C H

PATENT ASSIGNEE(S): (SEPR-N) SEPRACOR INC

COUNTRY COUNT: 95

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2001051453	A1	20010719	(200226) *	EN	55
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ					
NL OA PT SD SE SL SZ TR TZ UG ZW					
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM					
DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC					
LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE					
SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW					
AU 2001027793	A	20010724	(200226)		
US 6399826	B1	20020604	(200242)		
EP 1246789	A1	20021009	(200267)	EN	
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT					
RO SE SI TR					
US 2002183281	A1	20021205	(200301)		
JP 2003519675	W	20030624	(200341)		73
US 6710087	B2	20040323	(200421)		
AU 782567	B2	20050811	(200558)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2001051453	A1	WO 2001-US762	20010110
AU 2001027793	A	AU 2001-27793	20010110
US 6399826	B1 CIP of	US 1999-372158	19990811
		US 2000-480889	20000111
EP 1246789	A1	EP 2001-901941	20010110
		WO 2001-US762	20010110
US 2002183281	A1 CIP of	US 1999-372158	19990811
	Div ex	US 2000-480889	20000111
		US 2002-160033	20020604
JP 2003519675	W	JP 2001-551835	20010110
		WO 2001-US762	20010110
US 6710087	B2 CIP of	US 1999-372158	19990811
	Div ex	US 2000-480889	20000111
		US 2002-160033	20020604
AU 782567	B2	AU 2001-27793	20010110

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2001027793	A Based on	WO 2001051453
EP 1246789	A1 Based on	WO 2001051453
US 2002183281	A1 CIP of	US 6331571
	Div ex	US 6399826
JP 2003519675	W Based on	WO 2001051453
US 6710087	B2 CIP of	US 6331571
	Div ex	US 6399826
AU 782567	B2 Previous Publ.	AU 2001027793
	Based on	WO 2001051453

PRIORITY APPLN. INFO: US 2000-480889 20000111; US
1999-372158 19990811; US
2002-160033 20020604

AB WO 200151453 A UPAB: 20050912

NOVELTY - 1-(4-Chloro-phenyl)-cyclobutyl compounds (I), and their salts, solvates and clathrates are new.

DETAILED DESCRIPTION - 1-(4-Chloro-phenyl)-cyclobutyl compounds of formula (I) and their salts, solvates and clathrates are new.
R = alkyl.

INDEPENDENT CLAIMS are also included for the following:

- (1) a tartrate, mandelate or hydrochloride salt of (R)-desmethylsibutramine, (S)-desmethylsibutramine, (R)-didesmethylsibutramine or (S)-didesmethylsibutramine;
- (2) 1-(4-Chloro-phenyl)-cyclobutanecarbaldehyde of formula (II);
- (3) preparation of (1-(4-Chloro-phenyl)-cyclobutylmethylene)-methylamine (I; R = CH₃), comprising contacting cyclobutanecarbonitrile with diisobutylaluminum hydride to form an intermediate, reacting the intermediate with CH₃NH₂ to form (I; R=CH₃);
- (4) preparation method of racemic or optically pure desmethylsibutramine comprising contacting (I; R=CH₃), with a compound of formula AMX;
- (5) methods for preparing optically pure (R)- and (S)-desmethylsibutramine comprising contacting racemic desmethylsibutramine with (R)- or (S)- mandelic acid in a solvent of ethyl acetate and heptane to form the (R)- or (S)-mandelate salt of (R)- or (S)-desmethylsibutramine respectively;
- (6) preparing optically pure (R)- or (S)- didesmethylsibutramine comprising contacting racemic didesmethylsibutramine with (R)- or (S)- mandelic acid in a solvent of acetonitrile and methanol to form (R)- or (S)- mandelate salt of (R)- or (S)-didesmethylsibutramine respectively; and
- (7) treating or preventing neuropathic pain comprising administering a racemic or optically pure sibutramine metabolite or its salt, solvate or clathrate.

A = aryl, alkyl or aralkyl;

M = Li or Mg; and

X = halo.

ACTIVITY - Analgesic; Antidiabetic; Antidepressant; Nootropic; Tranquilizer; Antimanic; Neuroleptic; Anorectic; Neuroprotective; Antiparkinsonian; Anticonvulsant; Antiaddictive; Antidote; Antismoking; Gynecological; Antimigraine; Urothatic.

MECHANISM OF ACTION - Dopamine, **serotonin** and **norepinephrine reuptake inhibitor**.

In an assay to test the binding affinity of sibutramine metabolites, determined at the human recombinant norepinephrine uptake site, (-)-didesmethylsibutramine had an IC₅₀ of 6.2 nM, compared to (-)-sibutramine with an IC₅₀ value of 2500 nM.

USE - (I) and (II) are useful as intermediates for the synthesis of sibutramine metabolites. Sibutramine metabolites are useful for treating neuropathic pain, such as diabetic peripheral neuropathy, (claimed); they act as dopamine, **serotonin** and **norepinephrine reuptake inhibitors** and are also useful for treating or preventing erectile dysfunction, affective disorders (such as depression, attention deficit disorder, bipolar and manic conditions, dysthymic disorder and cyclothymic disorder), weight gain or obesity, cerebral function disorder (such as senile dementia, Alzheimer's type dementia, memory loss, amnesia/amnestic syndrome, disturbance of consciousness, coma, lowering of attention, speech disorders, Parkinson's disease, Lennox syndrome, autism, epilepsy, hyperkinetic syndrome and schizophrenia or cerebral function disorders induced by e.g. cerebrovascular diseases (such as cerebral infarction, cerebral bleeding, cerebral arteriosclerosis, cerebral venous thrombosis and head injuries)), pain (including chronic

and neuropathic pain e.g. thoracic outlet obstruction syndrome, compression and entrapment neuropathies, carpal tunnel syndrome, peroneal nerve palsy, radial nerve palsy and Guillain-Barre syndrome), obsessive compulsive disorder, substance abuse (e.g. cocaine and/or heroin abuse and nicotine addiction), eliciting smoking cessation, treating or preventing weight gain associated with smoking cessation, narcolepsy, chronic fatigue syndrome, seasonal affective disorder, fibromyalgia, premenstrual syndrome, anxiety, eating disorders, migraine or migraine headache and incontinence.

Dwg.0/0

L91 ANSWER 309 OF 313 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN

ACCESSION NUMBER: 2001-281941 [29] WPIX

DOC. NO. CPI: C2001-085874

TITLE: New biaryl compounds which inhibit
serotonin, norepinephrine and dopamine
reuptake used to treat e.g. hypertension,
depression, anxiety, phobias, eating disorders, headaches
and pain.

DERWENT CLASS: B03 B05

INVENTOR(S): ADAM, M D; HOWARD, H R

PATENT ASSIGNEE(S): (PFIZ) PFIZER PROD INC; (PFIZ) PFIZER INC

COUNTRY COUNT: 95

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2001027068	A1	20010419	(200129)*	EN	52
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ					
NL OA PT SD SE SL SZ TZ UG ZW					
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM					
DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC					
LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE					
SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW					
AU 2000073070	A	20010423	(200147)		
NO 2002001659	A	20020408	(200240)		
US 6410736	B1	20020625	(200246)		
BR 2000014733	A	20020611	(200248)		
EP 1220831	A1	20020710	(200253)	EN	
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT					
RO SE SI					
KR 2002040865	A	20020530	(200276)		
CZ 2002001180	A3	20021113	(200282)		
SK 2002000473	A3	20021203	(200282)		
CN 1378527	A	20021106	(200316)		
US 2003055038	A1	20030320	(200323)		
HU 2002003448	A2	20030228	(200330)		
JP 2003511434	W	20030325	(200330)		72
ZA 2002002804	A	20030625	(200348)		60
US 6596741	B2	20030722	(200354)		
MX 2002003793	A1	20021001	(200370)		
AU 769430	B	20040129	(200412)		
NZ 517696	A	20041224	(200506)		
EP 1220831	B1	20050608	(200543)	EN	
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT					
RO SE SI					
IN 2002000303	P3	20050318	(200548)	EN	
DE 60020726	E	20050714	(200549)		
ES 2240155	T3	20051016	(200571)		

MX 227531 B 20050429 (200571)

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2001027068	A1	WO 2000-IB1373	20000927
AU 2000073070	A	AU 2000-73070	20000927
NO 2002001659	A	WO 2000-IB1373	20000927
		NO 2002-1659	20020408
US 6410736	B1 Provisional Cont of	US 1999-167761P	19991129
		WO 2000-IB1373	20000925
		US 2000-692335	20001019
BR 2000014733	A	BR 2000-14733	20000927
		WO 2000-IB1373	20000927
EP 1220831	A1	EP 2000-960916	20000927
		WO 2000-IB1373	20000927
KR 2002040865	A	KR 2002-704767	20020413
CZ 2002001180	A3	WO 2000-IB1373	20000927
		CZ 2002-1180	20000927
SK 2002000473	A3	WO 2000-IB1373	20000927
		SK 2002-473	20000927
CN 1378527	A	CN 2000-814159	20000927
US 2003055038	A1 Provisional Provisional Cont of Div ex	US 1999-159276P	19991013
		US 1999-167761P	19991129
		WO 2000-IB1373	20000925
		US 2000-692335	20001019
		US 2002-153308	20020522
HU 2002003448	A2	WO 2000-IB1373	20000927
		HU 2002-3448	20000927
JP 2003511434	W	WO 2000-IB1373	20000927
		JP 2001-530089	20000927
ZA 2002002804	A	ZA 2002-2804	20020410
US 6596741	B2 Provisional Cont of Div ex	US 1999-167761P	19991129
		WO 2000-IB1373	20000925
		US 2001-692335	20011019
		US 2002-153308	20020522
MX 2002003793	A1	WO 2000-IB1373	20000927
		MX 2002-3793	20020415
AU 769430	B	AU 2000-73070	20000927
NZ 517696	A	NZ 2000-517696	20000927
		WO 2000-IB1373	20000927
EP 1220831	B1	EP 2000-960916	20000927
		WO 2000-IB1373	20000927
IN 2002000303	P3	WO 2000-IB1373	20000927
		IN 2002-MN303	20020311
DE 60020726	E	DE 2000-00020726	20000927
		EP 2000-960916	20000927
		WO 2000-IB1373	20000927
ES 2240155	T3	EP 2000-960916	20000927
MX 227531	B	WO 2000-IB1373	20000927
		MX 2002-3793	20020415

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2000073070	A Based on	WO 2001027068
BR 2000014733	A Based on	WO 2001027068

EP 1220831	A1 Based on	WO 2001027068
CZ 2002001180	A3 Based on	WO 2001027068
SK 2002000473	A3 Based on	WO 2001027068
US 2003055038	A1 Div ex	US 6410736
HU 2002003448	A2 Based on	WO 2001027068
JP 2003511434	W Based on	WO 2001027068
US 6596741	B2 Div ex	US 6410736
MX 2002003793	A1 Based on	WO 2001027068
AU 769430	B Previous Publ.	AU 2000073070
	Based on	WO 2001027068
NZ 517696	A Based on	WO 2001027068
EP 1220831	B1 Based on	WO 2001027068
DE 60020726	E Based on	EP 1220831
	Based on	WO 2001027068
ES 2240155	T3 Based on	EP 1220831
MX 227531	B Based on	WO 2001027068

PRIORITY APPLN. INFO: US 1999-167761P 19991129; US
 1999-159276P 19991013; US
 2000-692335 20001019; US
 2002-153308 20020522; US
 2001-692335 20011019

AB WO 200127068 A UPAB: 20010528

NOVELTY - Biaryl ether compounds of formula (I) and their salts are new.

DETAILED DESCRIPTION - Biaryl ether compounds of formula (I) and their salts are new:

n,m = 1-3;

R1, R2 = H, 1-4C alkyl, 2-4C alkenyl or 2-4C alknyl; or

NR1R2 = an optionally substituted heterocyclic ring; and

R3, R4 = H or 1-4C alkyl optionally substituted by 1-3 F atoms; or

CR3R4 = an optionally substituted carbocyclic ring; or

R2+R3 together with the N to which R2 is attached and the C to which R3 is attached form = an optionally substituted heterocycle;

X = optionally substituted phenyl, heteroaryl or heterocycle;

Y' = H, halo, optionally substituted 1-4C alkyl or alkoxy, CN, NO2, optionally substituted amino, optionally substituted aminosulfonyl or a thioether, alkylsulfinyl or alkylsulfonyl group; and

Z = H, halo, optionally substituted 1-4C alkyl or 1-4C alkoxy.

With the Proviso that Phenyl rings A and B can be replaced by naphthyl groups and when phenyl ring A is replaced by naphthyl the ethereal O and the C to which R3, R4 and NR1R2 are attached, are attached to adjacent C atoms of the naphthyl ring and neither of these adjacent ring C atoms is adjacent to a fused ring C atom of the naphthyl group.

For Full Definitions see DEFINITIONS FIELD.

INDEPENDENT CLAIMS are made for the following:

(1) a composition for treating a condition or disorder that can be treated by **inhibiting the reuptake of**

serotonin, dopamine or **norepinephrine** comprises:

(a) a compound (I) or its salt;

(b) an NK-1 receptor antagonist or a 5HT1D receptor antagonist or a salt thereof; and optionally

(c) a carrier; and

(2) a biaryl compound of formula (XVIII) is new:

Q = C(O)R3' or CN; and

R3' = H, 1-4C alkyl, OH, 1-6C alkoxy or NR1R2.

ACTIVITY - Hypotensive, antidepressant, tranquilizer, anorectic, antimigraine, analgesic, nootropic neuroprotective, antiparkinsonian, vasoconstrictor, gastrointestinal, neuroleptic and uropathic.

MECHANISM OF ACTION - **Serotonin**, dopamine and

norepinephrine reuptake inhibitors.

Compounds (I) all had IC50 values in vitro of about less than or equal to 250 nM for serotonin reuptake inhibition, 1000 nM for dopamine reuptake inhibition and 1000 nM for norepinephrine reuptake inhibition.

USE - (I) can be used to treat hypertension, depression, generalized anxiety disorder, phobias, posttraumatic stress syndrome, avoidant personality disorder, premature ejaculation, eating disorders, obesity, chemical dependencies, cluster headache, migraine, pain, Alzheimer's disease, obsessive-compulsive disorder, panic disorder, memory disorders, Parkinson's disease, endocrine disorders, vasospasm, cerebellar ataxia, gastrointestinal disorders, negative symptoms of schizophrenia, premenstrual syndrome, fibromyalgia syndrome, stress incontinence, Tourette's syndrome, trichotillomania, kleptomania, male impotence, attention deficit hyperactivity disorder, chronic paroxysmal hemicrania and headache.

Dwg.0/0

L91 ANSWER 310 OF 313 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
 ACCESSION NUMBER: 1999-517972 [43] WPIX
 DOC. NO. CPI: C1999-151201
 TITLE: New spiro-indane and spiro-indole derivatives are useful for the treatment of e.g. **pain**, migraine, **depression**, obesity, alcoholism and bulimia.
 DERWENT CLASS: B02 B03
 INVENTOR(S): EFANGE, S M N; MASH, D C
 PATENT ASSIGNEE(S): (MINU) UNIV MINNESOTA
 COUNTRY COUNT: 1
 PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
US 5948807	A	19990907	(199943)*		18

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
US 5948807	A	US 1997-922827	19970903

PRIORITY APPLN. INFO: US 1997-922827 19970903

AB US 5948807 A UPAB: 19991020

NOVELTY - Spiro-indane and spiro-indole derivatives (I) are new.

DETAILED DESCRIPTION - Spiro-indane and spiro-indole derivatives of formula (I) and their salts are new.

X, Y = thioxo, oxo or two hydrogens;

R1, R2 = H, halogen, OH, CN, N(Ra)(Rb) or 1-6C alkyl, 1-6C alkanoyl, 1-6C alkanoyloxy or 3-6C cycloalkyl (all optionally substituted by 1-3 V' groups);

Ra, Rb = H, 1-6C alkyl, 1-6C alkanoyl, phenyl, benzyl or phenethyl;

Z = N(Rd) or C(Re)(Rf);

Rc, Rd, Re, Rf = H, 1-6C alkyl or 3-6C cycloalkyl (both optionally substituted by 1-3 V' groups), aryl, aryl(1-6C)alkyl, 1-6C alkanoyl, arylcarbonyl or arylcarbonyl(1-6C alkyl);

aryl = aryl or heteroaryl ring optionally substituted on carbon atoms by 1-3 U' groups;

V' = halogen, NO2, CN, OH, 3-6C cycloalkyl, 1-6C alkoxy, 1-6C alkanoyl, 2-6C alkanoyloxy, C(O)ORm, C(O)NRnRo or NRlRq;

U' = halogen, NO2, CN, OH, trifluoromethyl, trifluoromethoxy, or 1-6C

alkyl, 3-6C cycloalkyl or 1-6C alkoxy (all optionally substituted by 1-3 V' groups), 1-6C alkanoyl, 2-6C alkanoyloxy, C(O)ORg, C(O)NRhRi or NRjRk; Rg, Rh, Ri, Rm, Rn, Ro = H or 1-6C alkyl; and Rj, Rk, Rl, Rq = H, 1-6C alkyl, 1-6C alkanoyl, phenyl, benzyl or phenethyl.

ACTIVITY - Analgesic; antimigraine; antidepressant; anorectic; antialcoholic; antiaddictive; nootropic; tranquilizer.

MECHANISM OF ACTION - Monoamine **reuptake inhibitor**; dopamine **reuptake inhibitor**; **serotonin reuptake inhibitor**; **norepinephrine reuptake inhibitor**.

In vitro tests at selected binding sites were carried out with radioligand binding techniques. 3-(3,4-Dichlorophenyl)-6-methoxyspiro(indan-1,3'-pyrrolidine) (Ia) gave IC50 value of 0.002 micro M at the SERT-1 (cocaine binding site on serotonin transporter), compared to a figure of 0.034 micro M for the antidepressant drug fluoxetine.

USE - As monoamine **reuptake inhibitors** (dopamine, **serotonin** or **norepinephrine reuptake inhibitors**) for the treatment of pain, headache or migraine (claimed). For the treatment of depression, obesity, sexual dysfunction, alcoholism, cocaine/opiate dependence, bulimia, anorexia nervosa, attention deficit hyperactivity disorder, obsessive-compulsive disorder and impulse control disorder.

ADVANTAGE - The compounds are inhibitors of monoamine reuptake useful for treating diseases where insufficient synaptic levels of monoamine are implicated.

Dwg.0/4

L91 ANSWER 311 OF 313 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
 ACCESSION NUMBER: 1990-107409 [14] WPIX
 DOC. NO. CPI: C1990-047250
 TITLE: New aryl-thio, -sulphonyl or -sulphonyl propan-amine
 cpds. - are selective **serotonin** and
norepinephrine uptake
inhibitors useful for treating e.g. obesity or
 depression.
 DERWENT CLASS: B03 B05
 INVENTOR(S): FOSTER, B J; HUNDEN, D C; LAVAGNINO, E R
 PATENT ASSIGNEE(S): (ELIL) LILLY & CO ELI
 COUNTRY COUNT: 16
 PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
US 4902710	A	19900220	(199014)*		12
EP 373836	A	19900620	(199025)		
R: AT BE CH DE ES FR GB GR IT LI LU NL SE					
CA 2005173	A	19900614	(199035)		
JP 02218661	A	19900831	(199041)		
EP 373836	B1	19940316	(199411)	EN	35
R: AT BE CH DE ES FR GB GR IT LI NL SE					
DE 68913930	E	19940421	(199417)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
US 4902710	A	US 1988-284501	19881214
EP 373836	A	EP 1989-312829	19891208

JP 02218661	A	JP 1989-324878	19891212
EP 373836	B1	EP 1989-312829	19891208
DE 68913930	E	DE 1989-613930	19891208
		EP 1989-312829	19891208

FILING DETAILS:

PATENT NO	KIND	PATENT NO
DE 68913930	E Based on	EP 373836

PRIORITY APPLN. INFO: US 1988-284501 19881214

AB US 4902710 A UPAB: 19930928

3-(Aryl-thio, -sulphinyl or -sulphonyl) propanamines of formula RS(O)n-CHR1-CH2CH2-NR2R3 (I) and their acid addn salts are new: where R = (opt. substd.) phenyl; (opt. substd.) naphthyl; or thienyl, furanyl or pyrrolyl (each opt. substd.: by halo or 1-4C alkyl); R1 = (opt. substd.) phenyl, 5-7C cycloalkyl, thienyl (opt. substd.: by halo or 1-4C alkyl), furanyl, pyridyl or thiazolyl; R2 and R3 = H or Me; and n = 0, 1 or 2.

Pre.f R = phenyl (opt. substd. by Me, MeO or CF3) or thienyl (opt. substd.: by Me). R1 = phenyl; n = 0; R2 = H; and R3 = Me.

USE - (I) are selective **serotonin** and **norepinephrine uptake inhibitors** which may be used to treat obesity, **depression**, alcoholism, **pain**, etc.
0/0

L91 ANSWER 312 OF 313 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN

ACCESSION NUMBER: 1989-159291 [22] WPIX

DOC. NO. CPI: C1989-070699

TITLE: New 3,4-di phenyl butan-amine cpds. - are selective inhibitors of serotonin and nor-epinephrine uptake, useful for treating e.g. depression obesity and anxiety.

DERWENT CLASS: B05

INVENTOR(S): ROBERTSON, D W; WONG, D T

PATENT ASSIGNEE(S): (ELIL) LILLY & CO ELI

COUNTRY COUNT: 14

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
EP 318233	A	19890531	(198922)*	EN	20
R: AT BE CH DE ES FR GB GR IT LI NL SE					
JP 02000235	A	19900105	(199007)		
US 4996235	A	19910226	(199111)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
EP 318233	A	EP 1988-311014	19881122
JP 02000235	A	JP 1988-299389	19881124
US 4996235	A	US 1987-125512	19871125

PRIORITY APPLN. INFO: US 1987-125512 19871125

AB EP 318233 A UPAB: 19930923

3-4-Diphenylbutanamines of formula (I) and their acid addition salts are new: R1, R2 = H or Me; R3-R6 = H, halo, CF3, 1-4C alkyl, 1-3C alkoxy or 2-4C

alkenyl.

N-methyl-3-phenyl-4-(4-trifluoromethyl phenyl)butanamine (Ia) and N-methyl-3-phenyl-4-(2-methylphenyl) butanamine are specifically claimed.

USE - (I) are potent, selective, **serotonin** and **norepinephrine uptake inhibitors**. Useful in the treatment of disorders associated with these neural systems e.g. obesity, **depression**, alcoholism, **pain**, loss of memory, anxiety and smoking. (I) also have good oral bioavailability. Dosage is 0.01-20 (0.1-5) mg/kg/day.
0/0

L91 ANSWER 313 OF 313 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
ACCESSION NUMBER: 1988-184588 [27] WPIX
DOC. NO. CPI: C1988-082330
TITLE: New 2-aryloxy-propan-amine derivs. - useful as inhibitors of serotonin and nor epinephrine uptake.
DERWENT CLASS: B03 B05
INVENTOR(S): KRUSHINSKI, J H; ROBERTSON, D W; WONG, D T
PATENT ASSIGNEE(S): (ELIL) LILLY & CO ELI; (KRUS-I) KRUSHINSKI J H; (ROBE-I) ROBERTSON D W; (WONG-I) WONG D T
COUNTRY COUNT: 27
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
EP 273658	A	19880706	(198827)*	EN	
R: AT BE CH DE ES FR GB GR IT LI LU NL SE					
AU 8782660	A	19880623	(198833)		
JP 63185946	A	19880801	(198836)		
DK 8706648	A	19880623	(198840)		
PT 86389	A	19890117	(198909)		
HU 47561	T	19890328	(198917)		
CN 87108175	A	19880706	(198929)		
ZA 8709472	A	19890830	(198939)		
US 4956388	A	19900911	(199039)		
EP 273658	B	19901031	(199044)		
R: AT BE CH DE ES FR GB IT LI LU NL SE					
DE 3765919	G	19901206	(199050)		
SU 1598865	A	19901007	(199125)		
US 5023269	A	19910611	(199126)		
ES 2019949	B	19910716	(199133)		
IL 84863	A	19920329	(199218)		
CA 1302421	C	19920602	(199228)		
PH 26556	A	19920819	(199634)		
JP 2549681	B2	19961030	(199648)	18	
BR 1100389	A3	19971007	(199746)		
KR 9603808	B1	19960322	(199912)		
DK 174599	B	20030714	(200353)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
EP 273658	A	EP 1987-311181	19871218
JP 63185946	A	JP 1987-322617	19871218
ZA 8709472	A	ZA 1987-9472	19871217
US 4956388	A	US 1990-462925	19900112
SU 1598865	A	SU 1987-4203804	19871217
US 5023269	A	US 1990-499940	19900327

CA 1302421	C	CA 1987-554601	19871217
PH 26556	A	PH 1987-36267	19871218
JP 2549681	B2	JP 1987-322617	19871218
BR 1100389	A3	BR 1997-1100389	19970430
KR 9603808	B1	KR 1987-14449	19871218
DK 174599	B	DK 1987-6648	19871217

FILING DETAILS:

PATENT NO	KIND	PATENT NO
JP 2549681	B2 Previous Publ.	JP 63185946
DK 174599	B Previous Publ.	DK 8706648

PRIORITY APPLN. INFO: US 1986-945122 19861222

AB EP 273658 A UPAB: 19930923

3-Aryloxy-propanamine derivs. of formula $R1-C(OAr)HCH_2CH_2NR_1R_2$ (I) and their acid-addition salts are new. $R1 = 5-7C$ cycloalkyl, thienyl, halothienyl, (1-4C)alkylthienyl, furanyl, pyridyl or thiazolyl; $Ar = Ph$ opt. substd. by 1 or 2 halogen, 1-4C alkyl, 1-4C alkoxy or CF_3 , or naphthyl opt. substd. by 1 halogen, 1-4C alkyl or CF_3 .

USE/ADVANTAGE - (I) **inhibit serotonin** and **norepinephrine uptake**. They may therefore be useful in treating obesity, **depression**, alcoholism, **pain**, loss of memory, anxiety, smoking etc. They have low toxicity. Dose is 0.05-10 mg/kg daily.